Lit - SSRIs - Akathisia

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Review

SSRI-Induced extrapyramidal side-effects and akathisia: implications for treatment

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The selective serotonin reuptake inhibitors (SSRIs) may occasionally induce extrapyramidal side-effects (EPS) and/or akathisia. This may be a consequence of serotonergically-mediated inhibition of the dopaminergic system. Manifestations of these effects in patients may depend on predisposing factors such as the presence of psychomotor disturbance, a previous history of drug-induced akathisia and/or EPS, concurrent antidopaminergic and/or serotonergic therapy, recent monoamine oxidase inhibitor discontinuation, comorbid Parkinson's disease and possibly deficient cytochrome P450 (CYP) isoenzyme status. There is increasing awareness that there may be a distinct form of melancholic or endogenous depression with neurobiological underpinnings similar to those of disorders of the basal ganglia such as Parkinson's disease. Thus, it is not surprising that some individuals with depressive disorders appear to be susceptible to developing drug-induced EPS and/or akathisia. In addition, the propensity for the SSRIs to induce these effects in individual patients may vary within the drug class depending, for example, on their selectivity for serotonin relative to other monoamines, affinity for the 5-HT_{2C} receptor, pharmacokinetic drug interaction potential with concomitantly administered neuroleptics and potential for accumulation due to a long half-life. The relative risk of EPS and akathisia associated with SSRIs have yet to be clearly established. The potential risks may be reduced by avoiding rapid and unnecessary dose titration. Furthermore, early recognition and appropriate management of EPS and/or akathisia is required to prevent the impact of these effects on patient compliance and subjective well-being. It is important that the rare occurrence of EPS in patients receiving SSRIs does not preclude their use in Parkinson's disease where their potentially significant role requires more systematic evaluation.

Key words: akathisia; basal ganglia; CYP2D6; dopamine; extrapyramidal side-effects; SSRIs; serotonin syndrome

Introduction

Extrapyramidal side-effects (EPS) and akathisia may be considered as disorders primarily of the dopamine (DA) system. Drugs such as the neuroleptics which act on the DA system are known to produce akathisia and EPS. However, many psychotropic drugs with pharmacological effects which do not directly induce dopaminergic mechanisms may occasionally also produce such side-effects. Perhaps, this is not surprising considering the interrelationship of neurotransmitter systems in the central nervous system (CNS). The serotonin system, in particular, has close associations with the DA system.

This paper will first review the potential of SSRIs, drugs which apparently enhance serotonin neurotransmission, to induce EPS and akathisia; second, give some guidelines for the prevention, early recognition and management of these effects; and third explore the pharmacodynamic mechanisms underlying these effects and possible differences in potential to induce these effects amongst the SSRIs.

SSRIs and EPS/akathisia

SSRIs and EPS

EPS (Table 1) may rarely be induced by SSRIs. They include dystonias, dyskinesias and bruxism (Table 2). In a retrospective incidence study of depressed geriatric in-patients (mean age 75–76 years), receiving SSRIs, four (6%) of 67 patients experienced an EPS, including akathisia, resting tremor, cogwheel rigidity and bradykinesia (Gormley *et al.*, 1997). Two of the patients had pre-existing Parkinson's disease. In reports of adverse reactions in 5555 patients given fluoxetine throughout New Zealand, there were 15 notifications of EPS probably or possibly caused by fluoxetine (Coulter and Pillans, 1995; Tables 2 and 3). The reactions included mild dystonia, tremor, leg spasms, trismus, torticollis, opisthotonus, akathisia and tardive dyskinesia. In the case series, two patients were also receiving lithium, four were receiving antipsychotics, two were receiving tricyclic antidepressants (TCAs), and one was receiving metoclopramide. Nine of the 15 patients were older than 65 years.

Table 1 Definition of terms used in this review

Akathisia	A syndrome characterized by an inner sense of restlessness and an inability to sit or stand still
Akinesia	Absence or loss of the power of voluntary movement
Basal ganglia	Striate body and cell groups associated with striate body, such as subthalamic nucleus and substantia nigra
Bradykinesia	A decrease in spontaneity and movement
Bruxism	Clenching or grinding of teeth (often occurs during sleep)
Dyskinesia	Abnormal involuntary movements characterized by insuppressible, stereotyped, automatic movements that cease only during sleep. They may be choreic (rapid, jerky, nonrepetitive), athetoid (slow, sinuous, continuous) or choreoathetoid and may affect any part of the body
Dystonia	A state of abnormal (either hypo- or more typically hyper-) tonicity in any musculature
Extrapyramidal effects	Usually describes abnormal movement arising from basal ganglia, its associated structures (substantia nigra, subthalamic nucleus) and its descending connections with the mid-brain. These brain structures affect bodily (somatic) movement
Myoclonus	One of a series of shock-like involuntary contractions of a group of muscles
Restlessness	Aimless motor activity that is poorly organized and represents a state of physical or mental unease. Related terms to describe phenomena that resemble, or overlap with restlessness include psychomotor agitation, fidgetiness, hyperactivity, jitteriness and behavioural activation. Akathisia describes a syndrome of restlessness
Striatum	Collective name for the caudate nucleus and putamen which together with the globus pallidus form the striate body
Tremor	Repetitive oscillatory movements caused by irregular contraction of opposing muscle groups
Trismus	Persistent contraction of the masseter muscles (i.e. a type of dystonia)

Although a definite association between SSRIs and EPS has not been established, in seven of the 15 patients in the case series of Coulter and Pillans (1995), fluoxetine was the only psychotropic agent used. That EPS disappeared or improved in 12 of the 15 patients after withdrawal of fluoxetine is also supportive evidence that fluoxetine was causally related. Furthermore, there are reported cases where fluoxetine administration alone (Bouchard *et al.*, 1989; Reccoppa *et al.*, 1990; Fleischacker, 1991; Black and Uhde, 1992; Steur, 1993; Mander *et al.*, 1994; Fitzgerald and Healy, 1995; Sandler, 1996), fluvoxamine alone (Arya and Szabadi, 1993; George and Trimble, 1993; Chong, 1995), paroxetine alone (Jimenez *et al.*, 1994; al-Adwani, 1995; Rone and Ferrando, 1996; Romanelli *et al.*, 1996), and sertraline alone (Shihabudden *et al.*, 1994; Lewis *et al.*, 1997), have been associated with EPS. There were predisposing factors present in many of these case reports, such as a history of previous brain damage (Shihabuddin *et al.*, 1994; al-Adwani, 1995; Coulter and Pillans, 1995; Rone and Ferrando, 1996), Parkinson's disease (Jimenez *et al.*, 1994; al-Adwani, 1995) and previous antidopaminergic therapy. In one patient receiving fluoxetine, acute dystonia recurred on rechallenge (Reccoppa *et al.*, 1990), and in one patient receiving paroxetine, diurnal bruxism recurred on challenge to four different SSRIs (Fitzgerald and Healy, 1995). A sertraline-treated patient who experienced mandibular dystonia had experienced an identical episode when administered trazodone (Lewis *et al.*, 1997). EPS have also been observed in depressed patients following discontinuation of fluoxetine (Stoukides and Stoukides, 1991) and paroxetine (D'Arcy, 1993).

Other antidepressants—especially amoxapine, but also TCAs, monamine oxidase inhibitors (MAOIs), bupropion and lithium have also been linked with EPS (Strouse *et al.*, 1993; Samuel, 1993; for review see Boyer and Feighner, 1991). The risk of SSRI-associated EPS relative to that of other antidepressants remains to be determined.

SSRIs and tardive dyskinesia

The apparent potential of SSRIs to induce EPS has prompted speculation that the drugs may induce persistent dyskinesias after long-term administration (Fishbain, 1996). Reports of SSRI-induced dyskinesia, variably persistent after SSRI discontinuation, have been described (Stein, 1991; Budman and Bruun, 1991; Scheepers and Rogers, 1994; al-Adwani, 1995; Coulter and Pillans, 1995; Fitzgerald and Healy, 1995; Botsaris and Sypek, 1996; Dubovsky and Thomas, 1996; Sandler, 1996). It is difficult to draw conclusions as almost all these cases were complicated by concomitant neurological disorders and/or concurrent or previous antidopaminergic therapy. However, Dubovsky and Thomas (1996) reported a 42-year-old woman who developed abnormal movements of tardive dyskinesia after 4 years of fluoxetine monotherapy. The increase in abnormal movements with both withdrawal of fluoxetine and addition of a dopaminergic agent, as well as the temporary suppression of movements with an increase in fluoxetine dosage, are consistent with tardive dyskinesia, as is the persistence of the abnormal movements long after discontinuation of all medications. Permanent withdrawal of fluoxetine was followed by a transient increase in abnormal movements, which gradually diminished in intensity but were still present a year later. During that year, the patient received no medication.

SSRIs and akathisia

One of the most serious EPS reported with the SSRIs is akathisia (Table 3). The term akathisia, derived from the Greek, literally means 'not sitting still'. Akathisia is a common side-effect of neuroleptics and the akathisia which is more rarely associated with antidepressant administration, including SSRI administration, appears to be milder but clinically indistinguishable from that of neuroleptic-induced akathisia (Zubenko *et al.*, 1987). There have been reports of SSRI-induced akathisia in patients who had previously developed akathisia during neuroleptic exposure (Lipinski *et al.*, 1989; Opler, 1994; Poyurovsky *et al.*, 1995a). Akathisia may occur during treatment with antidepressants from diverse pharmacological groups, including TCAs, MAOIs, SSRIs and nefazodone (Eberstein *et al.*, 1996). It has also been described with lithium (Poyurovsky *et al.*, 1995c), carbamazepine (Bodner *et al.*, 1995), following electroconvulsive therapy (ECT) (Poyurovsky *et al.*, 1995b), and as a consequence of withdrawal from antidepressant treatment (Sathananthan and Gershon, 1973). SSRI-induced akathisia is a relatively rare

Table 2 Literature reports of SSRI-induced extrapyramidal side effects

Reference	Patient	Drug(s)	Onset latency	Event(s)	Predisposing factor(s)
ADRAC (1996)	29-year-old female, depression	Paroxetine, 20 mg/day	4 h	Oral dyskinesia	—
ADRAC (1996)	22-year-old female, depression	Paroxetine, 20 mg/day	4 weeks	Involuntary facial movements, dysphonia, agitation	—
al Adwani (1995)	32-year-old male, depression	Paroxetine, 20 mg/day	Few days	Left sided dystonia	Previous left-hemiplegia
al Adwani (1995)	62-year-old female, depression	Paroxetine, 20 mg/day	3 weeks	Rigidity, bradykinesia, buccolingual dyskinesia	Parkinson's disease
Arya and Szabadi (1993)	38-year-old female, depression	Fluoxetine, 100 mg/day	2 months	Tic-like disorder, blinking, orofacial dyskinesia, mandibular dystonia	
Berk (1993)	26-year-old male, OCD	Paroxetine, 60 mg/day	3 months	Lingual dystonia, rigidity, salivorrhea	
Black and Uhde (1992)	39-year-old male, social phobia, panic disorder, depression	Fluoxetine, 80 mg/day	Few days	Dystonia	Recent dose increase, previous mild akathisia 2 weeks after initiating fluoxetine 20 mg/day
Botsaris *et al.* (1996)	81-year-old female, dementia, depression	Paroxetine, 10 mg/day	8 weeks	Buccolingual dyskinesia	Previous exposure to haloperidol
Botsaris *et al.* (1996)	81-year-old female, depression	Paroxetine, 20 mg/day	4 weeks	Buccolingual dyskinesia, truncal dyskinesia	Discontinuation of prochlorperazine 3 months previously
Bouchard *et al.* (1989)	47-year-old female, borderline personality disorder	Fluoxetine, 40 mg/day	—	Cogwheel rigidity, parkinsonism	Previous neuroleptic treatment
Bouchard *et al.* (1989)	45-year-old female, schizophrenia, melancholic depression	Fluoxetine, 20 mg/day	—	Cogwheel rigidity, tremor, akathisia	—
Brod (1989)	38-year-old female, depression	Fluoxetine, 20 mg/day	4 days	Rigidity	Muscular spasms due to cerebral palsy, previous neuroleptic treatment
Bud and Bruun (1991)	43-year-old female, schizophrenia disorder	Fluoxetine, 20 mg/day	8 days	Buccolingual dyskinesia	Previous neuroleptic treatment
Chong (1995)	38-year-old female, depression	Fluvoxamine, 100 mg/day	4–5 months	Mandibular dystonia	—
Coulter and Pillans (1995)	88-year-old female	Fluoxetine, 20 mg/day	13 days	Dystonia, torticollis	—
Coulter and Pillans (1995)	32-year-old male	Fluoxetine, 80 mg/day	7 days	Mild dystonia	—
Coulter and Pillans (1995)	81-year-old male	Fluoxetine, 60 mg/day	1 month	Coarse tremor of limbs	—
Coulter and Pillans (1995)	27-year-old female	Fluoxetine, 20 mg/day	4 months	Spasms right leg	Previous head injury, spastic tripiegia
Coulter and Pillans (1995)	71-year-old male	Fluoxetine 20 mg/day; thyroxine; ranitidine	1 month	Opisthotonus, rigidity	—
Coulter and Pillans (1995)	74-year-old female	Fluoxetine 20 mg/day; trifluoperazine 2 mg/day	14 days	Trismus	Concomitant neuroleptic treatment
Coulter and Pillans (1995)	49-year-old male	Fluoxetine, 40 mg/day; buspirone	3 months	Severe generalized tremor	Concomitant buspirone treatment
Coulter and Pillans (1995)	78-year-old male	Fluoxetine, 20 mg/day; famotidine; dipyridamole; aspirin	6 weeks	Tremor of arm and leg	—
Coulter and Pillans (1995)	70-year-old female	Fluoxetine, 20 mg/day; metoclopramide, 30 mg/day	1 month	Dystonia, tremor	Concomitant antidopaminergic treatment
Coulter and Pillans (1995)	67-year-old female, depression	Fluoxetine, 20 mg/day; carbamazepine; lithium; trimipramine; captopril	10 months	Dystonia	Overdose suspected
Coulter and Pillans (1995)	25-year-old male	Fluoxetine, 20 mg/day; pericyazine	5 months	Worsening leg spasms	Previous severe head injury
Coulter and Pillans (1995)	20-year-old female	Fluoxetine, 20 mg/day; pimozide, 6 mg/day; benztropine, 1 mg/day; nortriptyline, 50 mg/day	6 months	Tardive dyskinesia	Concomitant neuroleptic treatment

continued

Table 2 (continued)

Reference	Patient	Drug(s)	Onset latency	Event(s)	Predisposing factor(s)
Dave (1994)	54-year-old female, depression with hallucinations and akathisia	Fluoxetine, 20 mg day	4 weeks	Blepharospasm, dystonic posture, tremor of lip	Previous neuroleptic treatment
Danc *et al.* (1993)	66-year-old female, depression	Fluoxetine, 20 mg day; alprazolam, 1.5 mg day	2 days	Tremor, hypertonia, increased psychomotor retardation	–
Daniel *et al.* (1996)	18-year-old male	Fluoxetine, 20 mg day; risperidone, 2–3 mg day	1 week	Oro-buccal dyskinesia	Concomitant antipsychotic
Dubovsky and Thomas (1996)	38-year-old female, depression, PTSD	Fluoxetine, 60 mg day; doxepin, 150 mg day; lithium, 900 mg day	4 weeks	Orofacial, dyskinesia, bruxism	Concomitant lithium, similar dyskinetic movements on previous neuroleptic therapy
Dubovsky and Thomas (1996)	42-year-old female, depression	Fluoxetine, 60 mg day	4 years	Orofacial dyskinesia, athetoid hand movements	Similar movements 6 months after paroxetine 20 mg day and 6 weeks after fluoxetine 20 mg day
Dubovsky and Thomas (1996)	45-year-old female	Sertraline, 150 mg day	1 year	Orofacial dyskinesia	–
Eisenhauer and Jermain (1993)	12-year-old male, depression	Fluoxetine, 20 mg day	8 months	Numerous tics (i.e., eyelid blinking, shoulder hunching, movements of abdomen)	–
Ellison and Stanziani (1993)	36-year-old female, atypical depression, PTSD	Fluoxetine, 20 mg day	< 1 month	Nocturnal bruxism	–
Ellison and Stanziani (1993)	43-year-old female, depression	Fluoxetine, 15 mg day	< 2 weeks	Nocturnal bruxism, akathisia	–
Ellison and Stanziani (1993)	30-year-old female, depression dysthymia, PTSD	Fluoxetine, 20 mg day	< 2 weeks	Nocturnal bruxism	–
Ellison and Stanziani (1993)	36-year-old female, atypical depression, PTSD	Sertraline, 25 mg day	< 2 weeks	Nocturnal bruxism, night sweats, headache	–
Fallon and Liebowitz (1991)	38-year-old female, depression, systemic lupus erythematosis	Fluoxetine, 20 mg day	9 days	Truncal dyskinesia, leg restlessness	Monthly cyclophosphamide and metoclopramide on day 4–7 of fluoxetine therapy, white matter lesions on MRI and neuropsychological deficits
Fitzgerald and Healy (1995)	73-year-old female, anxiety	Sertraline, 100 mg day; flupenthixol, 1 mg day	2 weeks	Diurnal bruxism, restlessness	Recent dose reduction of flupenthixol, similar symptoms on paroxetine, fluvoxamine and clomipramine
Fitzgerald and Healy (1995)	28-year-old female, borderline personality disorder	Fluoxetine, 20 mg day	< 1 week	Diurnal bruxism	Previous neuroleptic treatment, similar symptoms on sertraline, paroxetine and fluvoxamine
Fitzgerald and Healy (1995)	67-year-old female, depression	Paroxetine, 20 mg day	11 months	Diurnal bruxism	Previous neuroleptic treatment, akathisia in response to risperidone
Fitzgerald and Healy (1995)	41-year-old female, depression	Fluoxetine, 20 mg day	< 1 week	Diurnal bruxism	–
Fitzgerald and Healy (1995)	30-year-old female, depression	Fluoxetine, 20 mg day	< 6 months	Nocturnal bruxism	–
Fitzgerald and Healy (1995)	61-year-old male, depression	Fluoxetine, 20 mg day	3 months	Diurnal bruxism, poor sleep, stomach churning, anxiety	Previous neuroleptic treatment recently discontinued

continued

Table 2 (continued)

Reference	Patient	Drug(s)	Onset latency	Event(s)	Predisposing factor(s)
Fox *et al.* (1997)	42-year-old female, depression	Paroxetine, 20 mg day	14 hours	Choreiform movements of all limbs, oculogyric crisis, hypotonia, tachycardia	
George and Trimble (1993)	36-year-old female, OCD and tic symptoms	Fluoxetine, 20 mg day	4 weeks	Mandibular dystonia	
Jimenez *et al.* (1994)	35-year-old male, depression	Paroxetine, 20 mg day	4 weeks	Masked facies, tremor, rigidity, postural instability, shuffling gait	Parkinson's disease
Jones-Feaning (1996)	12-year-old female, depression, panic disorder	Fluoxetine, 10 mg day	4 days	Orofacial dystonia, trismus, retrocollis, rigidity of upper extremeties	
Lock *et al.* (1990)	43-year-old female, depression	Fluoxetine, 20 mg day; perphenazine, 4 mg b.i.d.	2 weeks	Torticollis, cogwheel rigidity, hyperreflexia	Concomitant neuroleptic treatment
Marchiori *et al.* (1996)	74-year-old female, depression	Fluoxetine, 20 mg day	7 months	Ataxia, choreiform movements, orofacial dyskinesia	Deficient CYP 2D6 activity
Recoppa *et al.* (1996)	22-year-old female, depression	Fluoxetine, 40 mg day	10 days	Trismus, lingual and neck stiffness, anxiety	
Sandler (1996)	29-year-old male, OCD	Fluoxetine, 80 mg/day	12 months	Orofacial dyskinesia	
Scheepers and Rogers (1994)	24-year-old female	Fluoxetine, 20 mg/day	4 months	Limb-truncal, choreo-athetoid movements	Discontinued sulpiride 2.5 weeks previously
Scheepers and Rogers (1994)	45-year-old male, depression	Paroxetine, 20 mg/day	2 weeks	Dyskinetic movements and neck and limbs	Reemergence of movement disorder on fluoxetine and clomipramine
Scheepers and Rogers (1994)	30-year-old female, OCD, psychotic symptoms	Sertraline, 150 mg/day	4 weeks	Dyskinesia	Previous neuroleptic treatment, previous dyskinesia and akathisia on fluoxetine
Singh *et al.* (1995)	73-year-old male, depression	Fluoxetine, 20 mg/day; alprazolam, 0.5 mg nocte	2–3 days	Tremor, bradykinesia, rigidity, restlessness, disorientation	—
Shihabuddin and Rapport (1994)	35-year-old male, depression	Sertraline, 200 mg/day	3 days	Mandibular dystonia, restless legs, torticollis	Previous subarachnoid haemorrhage
Stein (1991)	39-year-old male, paranoid reactions	Fluoxetine, 20 mg/day; haloperidol, 5 mg/day	> 5 months	Buccolingual dyskinesia	—

OCD, Obsessive–compulsive disorder; PTSD, Post-traumatic disorder; MRI, magnetic resonance imaging.

event but is frequently unrecognized when it does occur. Following a recognized case of paroxetine-induced akathisia, Baldassano *et al.* (1996) reviewed their practice records and found that they had encountered three such cases among 67 paroxetine-treated patients.

In addition to the obvious motor (objective) manifestations of 'inability to sit still', most researchers agree that akathisia has a strong psychological (subjective) component. The precise definition of akathisia is a matter of controversy, as is the relative importance of the objective and subjective aspects of the disorder. Is akathisia a movement disorder or an intense and uncomfortable mental state (characterized by dysphoria and inner agitation) that builds to a level sufficient to compel non-specific motor manifestations? Sachdev (1995) gives an excellent description of the manifestations of akathisia (Table 4). The most outstanding feature of akathisia is the subjective distress. In its milder form, it is experienced as a vague feeling of apprehension, irritability, dysphoria, impatience or general unease. It is likely that dysphoria is an integral part of akathisia and in mild cases it may be the only symptom experienced (Chung and Chiu, 1996). Almost all patients describe a feeling of inner restlessness, especially if this description is suggested to them, and this may be referred to the mind or the body or both, but has a characteristic reference to the lower limbs. There is a strong urge to move the legs while sitting or standing, and pacing may be one consequence of this. The urge to move may be unrelenting and may preoccupy the person's thinking. Mild cases can often be detected by asking patients if they have difficulty in queuing at supermarkets, cooking a meal while standing, or sitting watching television. The amount of time a patient is able to stay in a particular position without being compelled to move may be an indication of the severity of akathisia.

Since the diagnosis of akathisia is a clinical diagnosis, the subjective and objective features must be distinguished from a number of other disorders producing similar subjective distress, with or without the motor features. Mild cases may present as non-specific dysphoria that may be wrongly interpreted by both sufferers and clinicians as part of the original psychiatric illness. Agitation may be a feature of both depression and mania. A non-agitated depression may appear to convert to an agitated form, if fluoxetine-induced akathisia is produced. In fact, in one group's opinion 'agitated depression and severe [fluoxetine-induced] akathisia are... indistinguishable and very likely share the same pathophysiology' (Lipinski *et al.*, 1989). Sweet *et al.* (1993) blindly

Table 3 Literature reports of SSRI-induced akathisia

Reference	Patient	Drug(s)	Onset latency	Event(s)	Predisposing factor(s)
Adler and Angrist (1995)	63-year-old, male, depression, panic disorder	Paroxetine, 20 mg day	—	Akathisia	Psychomotor agitation
ADRAC (1996)	86-year-old female, depression	Paroxetine, 20 mg day; felodipine, 5 mg day	5 months	Akathisia	—
Altshuler *et al.* (1994)	38-year-old female, depression	Sertraline, 50 mg day; trazodone, 50 mg as needed	5 weeks	Paraesthesia, dizziness, headaches, nausea, restlessness, anxiety, dyspnoea	Discontinued clomipramine 2 weeks previously
Baldassano *et al.* (1996)	18-year-old female, depression	Paroxetine, 20 mg day; clonazepam, 0.5 mg nocte	6 days	Dysphoria, insomnia, restless, anxious, moderate akathisia (Barnes Akathisia Scale)	-
Bangs *et al.* (1994)	14-year-old male, depression, conduct disorder	Fluoxetine, 20 mg day	6 weeks	Akathisia	—
Bertschy and Vandel (1993)	23-year-old female, bipolar depression	Fluoxetine, 40 mg day; carbamazzepine, 400 mg day	3 weeks	Akathisia, apathy	—
Coulter and Pillans (1995)	29-year-old male, schizophrenia	Fluoxetine, 20 mg day; haloperidol, i.m., 100 mg/month	7 days	Severe akathisia	Concomitant neuroleptic treatment
Coulter and Pillans (1995)	73-year-old female	Fluoxetine, 20 mg day; digoxin; frusemide; allopurinol; indomethacin	4 months	Akathisia, resting tremor	—
Hamilton and Opler (1992)	32-year-old female, depression, panic disorder	Fluoxetine, 50 mg day	3 weeks	Akathisia, suicidal ideation	—
Hoaken (1995)	78-year-old female, depression marked physical and cognitive anxiety	Sertraline, 100 mg day	Few days	Akathisia, rigidity	Previous exposure to clomipramine
Hofmann (1996)	60-year-old female, depressed	Citalopram, 20 mg/day	Few days	Akathisia, suicidal ideation, worsening of mood	—
Klee and Kronig (1993)	18-year-old female, depression	Sertraline, 25 mg day	3 days	Akathisia	—
Lipinski *et al.* (1989)	26-year-old female OCD	Fluoxetine, 60 mg/day	7 days	Insomnia, anxiety, akathisia	Similar more intense symptoms previously on neuroleptics
Lipinski *et al.* (1989)	22-year-old male, depression	Fluoxetine, 60 mg/day	5 days	Severe anxiety, akathisia	—
Lipinski *et al.* (1989)	35-year-old female, OCD	Fluoxetine, 20 mg/day	12 h	Anxiety, akathisia	Previous nocturnal myoclonic jerks on trazodone
Lipinski *et al.* (1989)	30-year-old female, OCD	Fluoxetine, 40 mg/day	2 days	Akathisia	Similar more intense symptoms previously on neuroleptics
Lavin *et al.* (1993)	30-year-old female, depressed, OCD, previous suicide attempts	Fluoxetine, 140 mg/day	3 days	Akathisia, persistent headache, worsening of mood, suicidal ideation	High dose, rapid titration over 1 week
La Porta (1993)	48-year-old female, refractory depression	Sertraline, 50 mg/day; thiothixene, 60 mg nocte	Few days	Anxiety, restlessness, akathisia	Concomitant neuroleptic treatment and oral/buccal dyskinesia
La Porta (1993)	46-year-old female, dysthymia	Sertraline, 50 mg/day	Few days	Akathisia	Fluoxetine, 20 mg day discontinued prior to initiation of sertraline
Muly *et al.* (1993)	36-year-old female, depression	Fluoxetine, 40 mg/day; lithium, 900 mg/day	Few days	Akathisia, hyperflexia, shivering, tremor, incoordination, myoclonus, diarrhoea	Concomitant lithium therapy
Olivera (1996)	40-year-old female, OCD and panic disorder	Paroxetine, 20 mg/day	3 days	Akathisia	Recent discontinuation on haloperidol

continued

Table 3 (*continued*)

Reference	Patient	Drug(s)	Onset latency	Event(s)	Predisposing factor(s)
Opler (1994)	34-year-old female, depression and psychosis	Sertraline, 50 mg/day; lithium, 800 mg/day; thiordazine, 150 mg/nocte	Few days	Akathisia	Previous akathisia on haloperidol
Poyurovsky *et al.* (1995a)	42-year-old male, OCD	Fluvoxamine, 300 mg/day	—	Akathisia, anxiety	Previous neuroleptic treatment, previous akathisia on haloperidol
Rothschild and Locke (1991)	25-year-old female, melancholic depression	Fluoxetine, 40 mg/day	6 days	Severe anxiety, akathisia, suicidal ideation	Previous suicidal ideation
Rothschild and Locke (1991)	47-year-old male, depression	Fluoxetine, 40 mg/day	5 days	Severe anxiety, akathisia	—
Rothschild and Locke (1991)	34-year-old female, depression	Fluoxetine, 40 mg/day	2 days	Akathisia	Previous suicide attempts
Settle (1993)	35-year-old female, panic disorder, agoraphobia, depressed	Sertraline, 50 mg/day	7 days	Tremulousness, restlessness, nervousness, motor restlessness, mild dysphoria, suicidal ideation	—
Tan (1996)	38-year-old male, OCD	Fluvoxamine, 300 mg/day; propanolol 60 mg/day	7 days	Akathisia	Previous clomipramine treatment

OCD, obsessive–compulsive disorder

examined 127 admissions to an acute psychogeriatric unit and found eight patients, seven of whom fulfilled criteria for major depression, previously unexposed to neuroleptics who presented with subjective akathisia type symptoms.

The 'jitteriness syndrome' reported in some patients with panic disorder when treatment with antidepressants, including SSRIs, is initiated, may resemble akathisia (Gorman *et al.*, 1987). Descriptions of the jitteriness syndrome, such as 'initial insomnia, jitteriness, shakiness, occasional racing thoughts, and a restlessness that made him feel he had to be moving' (Pohl *et al.*, 1986), resemble descriptions of SSRI-induced akathisia, and sugges: that the syndromes may share some aspects of their pathophysiology (Lipinski *et al.*, 1989). Akathisia has been reported in patients with panic disorder or marked anxiety who were initiated on SSRIs (Hamilton and Opler, 1992: Settle, 1993; Adler and Angst, 1995; Olivera, 1996, 1997).

Table 4. Signs and symptoms of akathisia (Sachdev, 1995)

- Subjective
  - Feeling of inner restlessness
  - Inability to remain still when standing or sitting
  - Inability to keep legs still
  - Distressing sensations in limbs
- Objective
  - Sitting
    - Semipurposeful/purposeless (normal) leg/feet movements
    - Shifting body position in chair
    - Inability to keep toes still
    - Semipurposeful hand/arm movements
  - Standing
    - Shifting weight from foot-to-foot and/or walking on the spot
    - Purposeless (normal) foot movements
    - Inability to remain standing on one spot (e.g. walking or pacing)
  - Lying down
    - Coarse tremor of legs/feet
    - Myclonic jerks of the feet
    - Semipurposeful or purposeless leg/feet movements
    - Inability to remain lying down

It has been suggested that SSRI-induced akathisia may be associated with the emergence of ego-dystonic suicidality (Lipinski *et al.*, 1989; Rothschild and Locke, 1991; Hamilton and Opler, 1992). The most consistent factor implicated in these anecdotal accounts of rare adverse reactions involving suicidal ideation and behavior during fluoxetine treatment was the development of akathisia with agitation, restlessness and dysphoria (Power and Cowen, 1992). In the case series of Teicher *et al.* (1990), these symptoms, in most cases, were attributed to a worsening of depression and the dosage increased as these symptoms developed.

It may be less of a question of patients experiencing fluoxetine-induced suicidal ideation, than patients feeling that 'death is a welcome result' when the acutely discomforting symptoms of akathisia are experienced on top of already distressing disorders. Hamilton and Opler (1992) stated that the term 'suicidal ideation' to describe the apparent suicidality associated with akathisia was misleading as the 'suicidal ideation' reported in patients receiving fluoxetine was a reaction to the side-effect of akathisia (i.e. unbearable discomfort and restlessness) and not true suicidal ideation as is typically described by depressed patients experiencing suicidal ideation. In the case reports of Rothschild and Locke (1991) three depressed patients developed severe akathisia and suicidal ideation. These symptoms disappeared within 72 h of discontinuing fluoxetine in one case and remitted on treatment with propranolol in the remaining cases. Although the reporting of cases of SSRI-induced akathisia or worsening of depression is often occasioned by the occurrence of suicidal ideation or behaviors, it has been suggested that suicidal ideation is not a frequent

accompaniment of serotonergic overstimulation.akathisia (Cain. 1992).

Predisposing factors

SSRIs and Parkinson's disease

Patients may be vulnerable to experiencing extrapyramidal reactions if their extrapyramidal system is already compromised. Parkinson's disease is a progressive disabling neurological disorder resulting from loss of DA-containing cells in the substantial nigra. The central features of this disorder are its motor manifestations, although a variety of behavioral disturbances, including depression, are also frequently comorbid with Parkinson's disease. Patients with underlying Parkinson's disease may be more likely to experience reactions when a SSRI is administered (Bouchard *et al.*, 1989; Brod, 1989; Chouinard and Sultan, 1992; Daric *et al.*, 1993; Steur, 1993; Jimenez *et al.*, 1994; Meco *et al.*, 1994; al Adwani, 1995; Orengo *et al.*, 1996; Simons, 1996; Gormley *et al.*, 1997). However, in the presence of such predisposition it is difficult to predict the occurrence or type of motor disorder. Patients suffering from idiopathic Parkinson's disease have been reported to tolerate a SSRI well (Caley and Friedman, 1992; McCance-Katz *et al.*, 1992; Durif *et al.*, 1995; Meara *et al.*, 1995). Caley and Friedman (1992) reported no exacerbation of Parkinson's symptoms in 20 patients and worsening of symptoms in three depressed patients with Parkinson's disease receiving up to 40 mg/day of fluoxetine. In an open study, in 21 patients with Parkinson's disease, Meara *et al.* (1995) found depression was effectively and safely treated with sertraline without deterioration in motor disability. Indeed, in the group of responders (60%) measures of upper limb akinesia indicated significant improvement over the 3-month treatment period.

There are good reasons to relate depressive symptoms in patients with Parkinson's disease to DA depletion. Greatly improved mood in patients with depression and Parkinson's disease in response to the psychostimulant methylphenidate was found in one well-designed study (Cantello *et al.*, 1989). The antidepressant effect of L-dopa in Parkinson's disease (Goodwin and Sack, 1974), also suggests DA deficiency may underlie parkinsonian depression. However, depression in Parkinson's disease is in no sense a pure DA deficiency syndrome and other monoamines such as serotonin and noradrenaline (NA) are also depleted (Mayeux *et al.*, 1988). The administration of the serotonin precursor, 5-hydroxytryptophan (5-HT), has been shown to effectively treat depression in Parkinson's disease (Mayeux *et al.* 1988).

Very few controlled studies have been published on the treatment of depression in Parkinson's disease and none of those available provide a reliable answer on how to treat it (Klaassen *et al.*, 1995). Without treatment, depression in Parkinson's disease can persist, exacerbating cognitive decline, physical disability, as well as hastening progression through the stages of the disease (Starkstein *et al.*, 1992). The putative role of serotonin in depression in Parkinson's disease patients suggests SSRIs may be theoretically of special value. The evidence from open studies (Caley and Friedman, 1992; McCance-Katz *et al.* 1992; Meara *et al.*, 1995), suggest SSRIs may be effective treatments for the depression associated with Parkinson's disease.

SSRIs and neuroleptics

Patients may be more vulnerable to experiencing EPS if they are receiving concomitant serotonergic and particularly antidopaminergic medication, such as neuroleptics and metoclopramide (Coulter and Pillans, 1995; Christensen and Byerly, 1996). It has been suggested that even remote exposure to neuroleptics may sensitize nigrostriatal dopaminergic responses to increased serotonergic input from the raphe nuclei (Budman and Bruun, 1991). However, studies in schizophrenic patients where the neuroleptic treatment regimen was augmented with fluoxetine (Goff *et al.*, 1995), fluvoxamine (Silver and Nassar, 1992), sertraline (Thakore *et al.*, 1996) or citalopram (Salokangas *et al.*, 1996) have reported improvements in symptoms, particularly negative symptoms, of schizophrenia with no exacerbation of EPS.

The findings of Caley and Friedman (1992) and Meara *et al* (1995), that patients with Parkinson's disease generally tolerate SSRIs well, are consistent with evidence suggesting that worsening of parkinsonism or akathisia is uncommon when SSRIs are added to a stable neuroleptic regimen in chronically ill schizophrenic patients. It has been suggested that exacerbation of EPS are more likely to occur early in the course of neuroleptic therapy (Goff *et al.*, 1995). The inhibitory effects of SSRIs on striatal DA function, which may underlie such adverse neurological effects, are most apparent when DA levels are elevated above baseline levels, typically during the first few weeks of neuroleptic therapy (Palfreyman *et al.*, 1993; Korsgaard *et al.*, 1985). Chronically ill patients on long-standing stable doses of neuroleptics may be at less risk for an exacerbation of EPS when SSRIs are added. However, worsening of parkinsonian symptoms, akathisia, tardive dyskinesia and psychosis has been reported when fluoxetine was added to neuroleptic therapy in patients with chronic schizophrenia (Bacher and Ruskin, 1991; Ames *et al.*, 1993).

There may be differences amongst the SSRIs in their ability to induce EPS when coadministered with neuroleptics due to pharmacokinetic considerations. EPS and akathisia in patients receiving neuroleptics are dose-related phenomena. SSRIs differ markedly in their ability to inhibit the cytochrome P450 (CYP) isoenzyme-mediated metabolism of neuroleptics. Thus, a pharmacokinetic interaction may have contributed to the experience of EPS in the patients in the fluoxetine case series of Coulter and Pillans (1995) who were also receiving neuroleptics. Many other reports of the coadministration of fluoxetine with neuroleptics and risperidone, have reported an apparent potentiation of EPS and/or the induction of akathisia (Tate, 1989; Bouchard *et al.*, 1989; Lock *et al.*, 1990; Bacher & Ruskin, 1991; Goff *et al.*, 1991; Stein, 1991; Ketai, 1993; Fitzgerald and Healy, 1995; Daniel *et al.* 1996; Bauer *et al.*, 1996; Benazzi, 1996; Brown, 1997).

Paroxetine has also demonstrated a clinically relevant interaction with neuroleptics with potentiation of EPS (Horrigan and Barnhill, 1994; Malek-Ahmadi and Allen, 1995; Ozdemir *et al.* 1996). Fluoxetine, norfluoxetine and paroxetine are potent inhibitors of CYP2D6 activity (Preskorn *et al.*, 1994; Alderman *et al.*, 1994). Sertraline, fluvoxamine

and citalopram have mild potential to inhibit CYP2D6 (Preskorn *et al.*, 1994; Ereshesky, 1996b). However, fluvoxamine potently inhibits other important cytochrome P450 isoenzymes, such as CYP1A2, which may also mediate the metabolism of neuroleptics (Lane, 1996). For example, haloperidol concentrations have been demonstrated to be approximately doubled by the addition of fluvoxamine (Daniel *et al.*, 1994).

Management of SSRI-induced EPS/akathisia

The risk factors for SSRI-induced EPS are summarized in Table 5 and treatment strategies found useful in the management of SSRI-induced EPS are summarized in Table 6. SSRI-induced EPS may increase with dosage increase (Bouchard *et al.*, 1989; George and Trimble, 1993), improve with dose reduction (Black and Uhde, 1992; Berk, 1993; George and Trimble, 1993; Chong, 1995), and usually disappear entirely following discontinuation. However, dyskinesias appear to behave somewhat differently from other EPS. They often only become manifest after many weeks or months of SSRI administration, do not appear to be dose related and may also take weeks or months to resolve following SSRI discontinuation. On the other hand, dystonia and classical parkinsonian-effects, like akathisia, are often manifest within days of SSRI initiation or dosage increase and disappear rapidly with dosage reduction or discontinuation of the SSRI. SSRI-induced dystonia and parkinsonian effects may be more likely than dyskinesia to be associated with concomitant akathisic symptoms or a history of akathisia (Black and Uhde, 1992; Shihabuddin and Rapport, 1994; Hoaken, 1995

EPS associated with SSRI administration also appear to respond to established pharmacological treatments for neuroleptic-induced EPS, such as anticholinergics, including benztropine, diphenhydramine, and tribexyphenidyl (Recoppa *et al.*, 1990; Black and Uhde, 1992; George and Trimble, 1993; Shihabuddin and Rapport, 1994; Dave, 1994; Singh *et al.*, 1995; Jones-Fearing, 1996; Fox *et al.*, 1997).

Bromocriptene was noted to help resolve Parkinsonian side-effects (Bouchard *et al.*, 1989), but has also been associated with increased dyskinetic movements (Dubovsky and Thomas, 1996). Ellison and Stanziani reported four cases of SSRI-induced nocturnal bruxism, which resolved in three cases with co-administration of buspirone (5–10 mg nocte), and in the fourth after decreasing the dose of SSRI. It was postulated that these cases may have arisen from an SSRI-induced exacerbation of nocturnal bruxism found normally in association with sleep. However, Fitzgerald and Healy (1995) described several cases of diurnal bruxism in patients receiving SSRIs, usually in association with concomitant or recent neuroleptic administration, in which buspirone was ineffective. These findings are consistent with those of Michelli *et al.* (1993) who reported that antidopaminergic drug exposure could result in diurnal bruxism, which responded poorly to interventions. Substitution with a TCA has also been found to be an effective strategy for the management of EPS induced by SSRIs (Shihabuddin and Rapport, 1994; Fitzgerald & Healy, 1995).

Table 5 Risk factors for SSRI-induced extrapyramidal side-effects

Previous or concomitant antidopaminergic treatment, e.g. haloperidol
Metoclopramide
Previous brain damage, e.g. stroke
Basal ganglia disease, e.g. Parkinson's disease
Concomitant serotonergic medication, e.g. lithium

Table 6 Treatment strategies found successful in SSRI-induced extrapyramidal side-effects

SSRI-discontinuation-dose reduction
Anticholinergics, e.g. benztropine
Bromocriptene
Buspirone
Switch to TCA e.g. nortriptyline

Akathisia may be prevented or avoided if attention is given to the risk factors listed in Table 7. The minimum recommended dose of SSRI in depression should not be exceeded (e.g. 20 mg/day of fluoxetine and paroxetine, 50 mg day of sertraline) until a reasonable trial of these lower doses has been achieved. Agitation, anxiety, nervousness and restlessness following the introduction of an SSRI or an increase in the dose may represent the development or the prodromal features of akathisia. Concomitant serotonergic medications may predispose to serotonin toxicity in general, and concomitant antidopaminergic medications, such as neuroleptics, may predispose to akathisia and EPS, particularly if recently initiated. Following MAOI treatment, SSRIs should not be administered for at least 2 weeks and should be initiated at low dose with close clinical monitoring. Loss of therapeutic effect after initial response, particularly if accompanied by side-effects of agitation, restlessnes and anxiety, may be due to serotonergic overstimulation and may be managed by dose reduction, possibly after a temporary treatment discontinuation, rather than by dosage increase.

Treatment strategies found useful for SSRI-induced akathisia are illustrated in Table 8. Akathisia should be managed by discontinuation of the SSRI, dosage decrease, or if close

Table 7 Risk factors for SSRI-induced akathisia

History of drug-induced akathisia
Concomitant neuroleptic therapy (especially high potency, recently initiated or rapid up-titration)
Concomitant serotonergic medication (especially recently initiated or dose increase)
MAOI discontinuation in previous 4 weeks
High dose SSRI
Undesirable pharmacokinetic profile of SSRI*
Treatment emergent agitation, restlessness, anxiety, manic reaction and/or insomnia
Symptoms of agitation and restlessness at treatment baseline.

MAOI, Monoamine oxidase inhibitor.
*Potential to appreciably inhibit the metabolism of concomitant neuroleptic and serotonergic medication, non-linear pharmacokinetics such that dose increases produce disproportionate increases in plasma levels, a long-acting active metabolite with potential for slow accumulation and substantially increased plasma levels in elderly compared to younger individuals.

Table 8 Treatment strategies found successful for SSRI-induced akathisia

Frequent follow-up; supportive and pyschoeducational
SSRI discontinuation, dose reduction divided doses
Switch to an SSRI with less potential to induce akathisia
β-blockers e.g. propranolol
Benzodiazepines e.g. lorazepam
Anticholinergics e.g. biperiden
Antiserotonergic e.g. low-dose mianserin, cyproheptadine
Buspirone

clinical monitoring is possible, by continuation of the SSRI with the addition of propranolol, short-term benzodiazepine treatment or possibly low-dose mianserin. Mild cases may resolve with continued treatment (Olivera, 1997). However, symptoms of akathisia have been noted to persist for over 1 year in patients receiving fluoxetine, suggesting that at least in some patients tolerance to this side-effect may not develop (Lipinski *et al.*, 1989). Switching from fluoxetine to another SSRI which has less potential to induce akathisia is another possible strategy (Bauer *et al.*, 1996). However, a suitable wash-out period, perhaps at least 2 weeks, should be employed after discontinuing fluoxetine (Lane and Fischler, 1995). Antidepressant-induced akathisia is reversible upon discontinuation or dose reduction of the drug (Rothschild and Locke, 1991; Hamilton and Opler, 1992; Bertschy and Vandel, 1993; La Porta, 1993; Bangs *et al.*, 1994; Coulter and Pillans, 1995; Hoaken, 1995). It also appears to respond to established pharmacological treatments for neuroleptic-induced akathisia (Zubenko *et al.*, 1987). β-blockers have been used successfully in patients with SSRI-induced akathisia (Lipinski *et al.*, 1989; Rothschild and Locke, 1991; Klee and Kronig, 1993; Adler and Angrist, 1995; Baldassano *et al.*, 1996), as have benzodiazepines (La Porta, 1993; Settle, 1993; Altshuler *et al.*, 1994;).

Low-dose mianserin (15 mg at night), a 5-HT_{2A} 5-HT_{2C} 5-HT_3, pre-synaptic α_2-adrenoreceptor antagonist, has also been shown to be effective in SSRI, ECT and lithium-induced akathisia (Poyurovsky *et al.*, 1995a–c). Cyproheptadine was also effective in a case of akathisia induced by the addition of lithium to fluoxetine treatment (Muly *et al.*, 1993). Cyproheptadine has anticholinergic properties, but the beneficial effects of cyproheptadine are thought to be due to its marked antiserotonergic activity.

The usefulness of anticholinergic agents is not as well established in treating akathisia. They have been demonstrated to be effective in neuroleptic-induced akathisia (Adler *et al.*, 1993). However, Braud *et al.* (1983) found better response to anticholinergic drugs when akathisia was accompanied by drug-induced parkinsonism. In a case of SSRI-induced akathisia accompanied by dystonia the administration of anticholinergics relieved dystonia, but not akathisia (Shihabuddin and Rapport, 1994). However, anticholinergics have also been found to be effective in SSRI-induced akathisia with (Singh *et al.*, 1995), and without accompanying parkinsonian symptoms (Klee and Kronig, 1993; Tan, 1996).

The addition of buspirone has also been found to be effective in relieving SSRI-induced akathisia (Ellison and Stanziani, 1993). Buspirone, in addition to partial agonist effects at 5-HT_{1A} receptors, interacts with DA receptors (Gelenberg *et al.*, 1991).

Pharmacodynamic mechanisms

Serotonin–DA interactions

The pathogenesis of SSRI-induced EPS, which may be heterogenous, is unknown. One possible explanation is a direct effect of the serotonergic system. In addition to innervation of secondary motor areas in the brain, such as the extrapyramidal system (basal ganglia), the serotonergic system also innervates primary motor areas (Steinbusch, 1981). Innervation is heterogenous with preferential innervation of motor neurons projecting to axial rather than distal musculature. In the brainstem, 5-HT neurons densely innervate the motor neurons which project to the large muscles of the jaw, face and neck, but there is little innervation of the extraocular muscles (Steinbusch, 1981). The distribution of serotonergic neurons is associated with structures involved in movements using gross skeletal muscles and facial muscles rather than those involved in fine somatosensory discrimination. A role for the serotonergic system in coordinating sensory and automatic functions has been proposed by Jacobs and Fornal (1993).

It has also been suggested that SSRI-induced EPS may be caused by serotonergically mediated inhibition of dopaminergic transmission (Meltzer *et al.*, 1979; Bouchard *et al.*, 1989). DA associated functions in the brain are mediated through three distinct pathways. The dopaminergic system arises from a group of cells in the midbrain. Neurons from the substantia nigra ascend to the striatum via the nigrostriatal pathway, and are involved in the control of complex muscular movements and posture. Reduced DA neurotransmission in this pathway cause the stiffness, tremor and muscular dyscoordination of parkinsonism. A second pathway, the tuberoinfundibular tract, is associated with the production and release of prolactin. Neurons from the ventral tegmental area project in a third pathway, or set of pathways, the mesolimbic (to the limbic region comprising the caudate, putamen, nucleus accumbens, septum and substantia inominata (Nauta, 1986)) and mesocortical (to the cortical region).

The serotonergic neurons also arise from discrete midbrain nuclei; the dorsal raphé nucleus and the median raphé nucleus provide the most prominent projections. The median raphe nucleus projects to the limbic regions. Serotonergic projections from the dorsal raphé project directly to the basal ganglia and inhibit the firing of the dopaminergic neurons (Jacobs and Azmitia, 1992). This inhibition of the DA neurons in the striatum and substantia nigra by serotonin appears to be mediated by 5-HT_2 receptors (Ugedo *et al.*, 1989; Muramatsu *et al.*, 1988).

The concept of serotonergic modulation of DA function is supported by *in vivo* studies in animal models (Korsgaard *et al.*, 1985; Dewey *et al.*, 1995). For example, positron emission tomography (PET) studies in baboons showed that a 5-HT_2 antagonist (altanserin) increased the release of endogenous DA, while citalopram, a SSRI, decreased the release of endogenous DA (Dewey *et al.*, 1995). Furthermore, paroxetine was reported to induce oral hyperkinesia in the monkey (Korsgaard *et al.*, 1985) and to weakly potentiate haloperidol-induced symptoms of parkinsonism and dystonia. A preclinical study found that chronic fluoxetine treatment caused decreases in DA levels in the nucleus accumbens and striatum

in rats of between 60 and 70 percent that persisted for up to 14 days after fluoxetine was discontinued (Gardier *et al.*, 1994).

The interaction of serotonin- and DA-mediated neurotransmission is extremely complex and may be influenced by the relative activity of each system. Some additional studies have failed to demonstrate SSRI inhibition of DA turnover and others have actually demonstrated augmentation (for review see Beasley, 1994; Tiihonen *et al.*, 1996). It is likely that different 5-HT receptor subtypes, which may vary in their distribution within the basal ganglia, may mediate different effects on the DA system. For example, activation of 5-HT_2 receptors has an apparent inhibitory effect, whereas 5-HT_3 agonists appear to increase DA release (Blandina *et al.*, 1988). Furthermore, serotonin also has a direct influence on the cholinergic and γ-aminobutyric acid (GABA) system, and some of serotonin's effects on the DA system may be mediated, indirectly, through its modulation of the GABA and cholinergic systems (Dewey *et al.*, 1993a,b). Perhaps it is this complexity that explains the clinical heterogeneity, i.e. the finding that only a small subset of patients treated with SSRIs experience EPS. However, the study of serotonergic modulation of DA function has implications for etiologic and treatment mechanisms in several neuropsychiatric disease states, including schizophrenia, affective disorders and obsessive–compulsive disorder. It has been hypothesized that an imbalance between serotonin and DA systems occurs in these disease states, in part on the basis of the greater therapeutic efficacy of treatments that alter both systems rather than each system individually (Deutsch *et al.*, 1991; Brown and Gershon, 1993; McDougle *et al.* 1994).

The basal ganglia and depression

In the last few years there have been major advances in the understanding of basal ganglia function. There has been an increasing awareness of both the centrality of psychomotor deficits in melancholic-type depression and the striking clinical parallels between melancholia and certain basal ganglia disorders such as Parkinson's disease and Huntington's chorea (Rogers *et al.*, 1987; Parker and Hadzi-Pavlovic, 1996). The possibility exists that melancholia may be appropriately viewed as a neurological disorder in its own right and that the mechanisms leading to the motor, cognitive and mood changes in certain neurological disorders may also be involved in creating similar, albeit characteristically individual, combinations of such features in melancholia (Austin and Mitchell, 1996). Cummings (1992) proposed that the motor manifestations (affecting posture, gait and speech) of depression were similar to those in Parkinson's disease, where such features appear to be mediated by the basal ganglia (posture, gait and speech) and the right frontal cortex (speech). The clinical presentation of melancholia has much in common with the 'subcortical dementia' presentation that often characterizes disorders affecting the basal ganglia such as Parkinson's disease and Huntington's chorea, which are characterized by slowed mentation and movement, apathy, depression and reduced ability to manipulate acquired knowledge in the absence of so-called cortical deficits such as apraxia, agnosia and dysphasia (Albert *et al.*, 1974). In addition to subcortical deficits, significant 'frontal' executive deficits are also noted in these disorders.

Recent estimates suggest that approximately 40–50 percent of Parkinson's disease patients experience depression during the course of the disorder (Cummings, 1992). Recent studies employing a number of diverse methods have indicated that the prefrontal cortex and basal ganglia may be important in depression, particularly in elderly patients. Studies using MRI have revealed an increase in lesions of the basal ganglia in elderly depressed patients (Coffey *et al.*, 1990) and in depressed patients in both elderly and non-elderly age groups. An excess of hyperintensities has been observed in the basal ganglia–thalamocortical circuit fibres (Krishnan *et al.*, 1988; Hickie *et al.*, 1995; Salloway *et al.*, 1996). Decreased volume of the putamental and caudate nuclei has been observed in depressed patients (Krishnan *et al.*, 1992). PET scanning has shown significantly decreased glucose metabolism in the basal ganglia of patients with depression (Buchsbaum *et al.*, 1986; Baxter *et al.*, 1989). Also, stroke victims in whom the caudate nucleus is affected appear to have a higher frequency of major depression than those with strokes affecting other areas (Starkstein *et al.*, 1987; Mendez *et al.*, 1989).

Although the basal ganglia were previously thought to be involved only in the modulation of movement, it has been proposed that several parallel neural networks originate in the prefrontal cortex and pass through the basal ganglia, and that some of these networks may be involved in mood or cognitive function and others in movement. Mood disorders could result from dysfunction of one such network, for example a 'limbic loop' linking the ventral striatal nucleus of the basal ganglia to medial prefrontal cortical structures, whereas cognitive dysfunction could result from impairment of a 'prefrontal loop' linking the caudate nucleus with lateral prefrontal structures (Alexander *et al.*, 1986). This hypothesis may explain the lack of correlation between motor disability and cognitive impairment in patients with Parkinson's disease (Cooper *et al.*, 1991). Cognitive deficits in Parkinson's disease tend to be associated with concurrent depression (Starkstein *et al.*, 1989), and this correlation of cognitive deficits and depression severity has also been reported in endogenously depressed patients (Austin *et al.*, 1992b), and patients with late-life-onset major depression (Salloway *et al.*, 1996).

It is clear that depression frequently occurs in patients with disorders affecting the basal ganglia such as Parkinson's disease, that the bradykinesia of melancholia is indistinguishable from that seen in Parkinson's disease, and that a distinct subcortical pattern of cognitive deficits is common to both disorders. Both functional and structural disruption of the relevant brain regions or neural networks may be responsible for variation in the clinical presentation of melancholia. Recurrent episodes of melancholic depression with full recovery between episodes may reflect intermittent periods of abnormal function in genetically vulnerable individuals. In contrast, treatment resistance or lack of full recovery often seen in patients with predominantly late onset melancholia may be explained by structural, and thus potentially irreversible, disruption in these functional networks. The recent MRI studies of elderly depressed subjects identifying deep white matter and subcortical grey matter hyperintensities would support the possibility of such structural lesions. Where the lesions themselves are of insufficient severity to lead to symptoms, the addition of a stressor such as a negative life

event might be required for depression to occur (Krishnan, 1993b).

Studies of the prevalence of extrapyramidal signs in neuroleptic-naive, first episode schizophrenic patients indicate that extrapyramidal signs are present in approximately 20 percent (Caliguri *et al.*, 1993; Chatterjee *et al.*, 1995; Gupta *et al.*, 1995), suggesting the involvement of basal ganglia pathology in the schizophrenic process. The involvement of basal ganglia pathology in depression indicates that depressed patients may also be more vulnerable than non-depressed subjects to extrapyramidal reactions. Reduction of dopaminergic transmission induced by SSRIs could account for acute EPS and akathisia, while chronic decreases in dopaminergic transmission could result in hypersensitivity of post-synaptic DA receptors, which is postulated to be involved in tardive dyskinesia (Fishbain *et al.*, 1992). Consistent with this possibility, chronic treatment with fluoxetine has been demonstrated to up-regulate D_1 and D_2 receptors in mesolimbic terminals (Hammer *et al.*, 1993).

Is akathisia a serotonin syndrome?

'Dopamine–acetylcholine imbalance' was first conceptualized as the underlying pathophysiology of akathisia. This was due to the fact that akathisia is commonly induced by DA antagonists and is associated with idiopathic Parkinson's disease. However, parkinsonism and dystonia are characteristic side-effects of neuroleptics and although they usually accompany neuroleptic-induced akathisia, they are usually absent in antidepressant-induced akathisia. The exact pathophysiology of akathisia is far from clear, and whether it should or should not be considered an EPS is still an unsolved issue (Casey, 1994).

The nigrostriatal system is the largest projection of DA neurones to the forebrain and enhanced serotonergic neurotransmission occasionally produces EPS via an inhibition of DA neurotransmission in this pathway. However, there is a second, smaller projection of DA neurons to the forebrain in the mesocorticolimbic system. It is through enhanced, serotonin (and/or NA) mediated, inhibition of the DA neurones of this system that SSRI-induced akathisia is thought to be mediated (Lipinski *et al.*, 1989). It has been suggested (Marsden and Jenner, 1980), that the mesocorticolimbic DArgic pathway is involved in the pathophysiology because this pathway has been shown in animal models to be responsible for an inhibitory effect on motor activity. Bilateral lesions of the ventral tegmental area, which contains the DA neuron cell bodies of this pathway, can induce a behavioral equivalent of akathisia in rats characterized by permanent locomotor hyperactivity and a reduction in attention span (Tassin *et al.*, 1978). Serotonergic and noradrenergic input on the ventral tegmental area may have an inhibitory effect on DA neurotransmission and hence lead to hypofunction of the mesocorticolimbic pathway (Lipinski *et al.*, 1989). This model explains antidepressant-induced akathisia and positive treatment response to 5-HT_2 antagonists and β-adrenergic antagonists (Poyurovsky *et al.*, 1995a; Baldassano *et al.*, 1996). This hypothesis fits with the results of preclinical studies which have shown that high dose propranolol increases DA neurotransmission in the mesocorticolimbic pathway but not in the nigrostriatal pathway (Wiesel, 1976; Fuxe *et al.*, 1976).

Serotonergic drugs may have differential effects on the DA neurons of the nigrostriatal and mesocorticolimbic systems at different doses. For example, Goldstein *et al.* (1987a,b) demonstrated that at low doses 5-HT_2 receptor antagonists increased firing rates of DA neurons in the mesocorticolimbic system but not in the nigrostriatal system, whereas at higher doses, these agents increase firing rates of DA neurons in both systems. The differing and dose-dependent effects of 5-HT_2 receptor antagonists on DA neurons of the two main DA projection systems may be the reason that SSRI-induced akathisia is only rarely accompanied by parkinsonian symptoms. That is, the doses of fluoxetine and the SSRIs used in clinical practice may be sufficient to enhance serotonin-mediated inhibition of DA neurotransmission in the mesocorticolimbic system (rarely to produce akathisia but more commonly to produce side-effects of agitation, nervousness, manic reaction, etc.), but not sufficient to inhibit DA neurotransmission in the nigrostriatal system except in susceptible individuals.

SSRI-induced akathisia may represent a form of serotonergic overstimulation or serotonin toxicity (Cain, 1992). The serotonin syndrome is also thought to arise from acute serotonergic overstimulation when SSRIs or other serotonergic medication, are administered in combination with other medications acting via serotonergic mechanisms. This serotonin toxicity syndrome includes changes in mental status and behavior, neuromuscular system changes and autonomic instability (Lane and Baldwin, 1997). Agitation, restlessness and insomnia are commonly seen in cases of the serotonin syndrome and may be early prodromal signs of the syndrome (Bodner *et al.*, 1995). Tremor, myoclonus and hyperreflexia are also invariably present. Jaw jerking and dystonia (Noveske *et al.*, 1989; Feighner *et al.*, 1990; Muly *et al.*, 1993; Lappin and Auchincloss, 1994), dyskinesia (Sovner and Wolfe, 1988; Lappin and Auchincloss, 1994; Bodner *et al.*, 1995), and akathisia (Muly *et al.*, 1993) have also been reported. Some cases in which EPS have been described following SSRI administration may be part of, or a mild form of, a serotonin syndrome (Dursun *et al.*, 1993; Dursun *et al.*, 1995). In a suggested revision of the Sternbach criteria (Sternbach, 1991), for the diagnosis of the serotonin syndrome, Radomski, *et al.* (1995) included akathisia, oculogyric crisis and choreiform movements as additional clinical features of the syndrome.

The co-administration of serotonergic medications often leads to an increase in side-effects of insomnia, agitation, nervousness, manic reaction, etc. in addition to rarely inducing akathisia (Hopwood, *et al.*, 1993). In an open study 50 patients with refractory depression receiving 20 mg/day of fluoxetine or paroxetine were co-administered increasing doses of moclobemide to a maximum of 600 mg/day. The 50 patients receiving SSRIs, co-administered moclobemide, reported numerous treatment-emergent adverse events, including insomnia (64%), dizziness and ataxia (30%), myoclonic jerks (14%), confusion (12%), diaphoresis (12%), akathisia (10%) and one patient experienced the serotonin syndrome (Hawley *et al.*, 1996). Co-administration of lithium and SSRIs has been reported to produce akathisia (Muly *et al.*, 1993; Opler, 1994). In addition, a significantly higher incidence of adverse

experiences such as anxiety, insomnia and nervousness were reported when patients who had discontinued fluoxetine treatment were immediately initiated on paroxetine treatment compared to patients initiated on paroxetine treatment after a placebo wash-out period of 2 weeks (Lane and Fischler, 1995). The increased incidence of adverse events in the immediate switch group is indicative of enhanced serotonergic activity in this group due to the administration of paroxetine to patients with significant levels of circulating fluoxetine and norfluoxetine. The onset of a serotonin syndrome and mandibular dystonia was reported in a patient initiated on paroxetine (20 mg day) after discontinuing fluoxetine (20 mg day) 2 days earlier (Mills, 1995). In one case of akathisia after a few days of sertraline (50 mg day) administration, fluoxetine (20 mg/day) had been discontinued prior to the initiation of sertraline (La Porta, 1993).

The greatest potential for a serotonin syndrome appears to exist when a potent serotonin reuptake inhibitor is co-administered with a MAOI (Lane and Baldwin, 1997). Some of the reported cases of fluoxetine-induced akathisia occurred after a comparatively brief period of withdrawal from MAOIs (Teicher *et al.*, 1990). It has been proposed that previous MAOI treatment may predispose patients to the development of serotonin toxicity (Berkley, 1990; Brewerton, 1991). The minimum MAOI wash-out period recommended before beginning an SSRI is currently 2 weeks, however, persisting MAOI inhibition may be pharmacologically demonstrable for at least 4 weeks after cessation of treatment (Insel *et al.*, 1982).

The overlap between symptoms of the serotonin syndrome (Sternbach, 1991), akathisia (Sachdev, 1995) and the neuroleptic malignant syndrome (Levenson, 1985), mean that they are likely to share similar underlying pathophysiology and may respond to similar treatments. They may represent a spectrum of adverse effects that occur when there is an alteration in the balance between serotonin and DA in the CNS: symptoms of the neuroleptic malignant syndrome occurring in association with antidopaminergic agents, symptoms of the serotonin syndrome occurring in association with antiserotonergic agents and symptoms of akathisia occurring with both types of agents. In many cases symptoms will fulfill the accepted definitions for two or all three of these disorders.

Possible SSRI differences

Whilst serotonin reuptake inhibition is the most striking characteristic of all the five widely marketed SSRIs, other receptor and reuptake activity may explain the more subtle differences between the five compounds (Hale, 1996). Amongst the SSRIs, differences in efficacy are emerging in subgroups of depressed patients, such as patients with psychomotor agitation and melancholic depression. As previous discussion in this review has demonstrated, these patients may have similar underlying pathophysiology to that underlying SSRI-induced EPS and akathisia. In addition, the pharmacokinetics of the SSRIs vary markedly amongst the group. This means that the ability of an SSRI to deliver a predictable effect site concentration will also vary widely within the group.

The relative potential for the different SSRIs to cause certain extrapyramidal effects may vary. The UK Committee on Safety of Medicines (CSM, 1993; Choo, 1993), for example, has warned that orofacial dystonia was being reported more frequently with paroxetine than with other SSRIs. In most cases, the reactions occurred after several days of treatment and were self-limiting. A comparison of the post-marketing safety profiles of SSRIs using spontaneous adverse drug reaction (ADR) report data from the Adverse Drug Reaction On-Line Information Tracking (ADROIT) database again revealed that neurological ADRs (such as dystonia and tremor) were more common with paroxetine and psychiatric ADRs (such as agitation, aggression, suicidal ideation) were more common with fluoxetine (Price, Waller and Wood, 1996). Furthermore, 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 10000 patients in each SSRI cohort) (MacKay *et al.*, 1997). Tremor was reported significantly more often in the first month after starting therapy with paroxetine or fluvoxamine, than with sertraline or fluoxetine.

SSRIs: serotonin vs DA and NA

The SSRIs differ in their selectivity for monoamine reuptake mechanisms. Paroxetine is the most selective for serotonin vs DA reuptake inhibition (Bolden-Watson and Richelson, 1993; Hyttel, 1993; Table 9). Sertraline is an inhibitor of DA uptake *in vitro* with an IC_{50} of 48 nm (Hyttel, 1993). No other SSRI shows a similar profile: Fluoxetine and paroxetine are the next most potent DA reuptake inhibitors with IC_{50}s of 5000 and 5100 nm respectively. Sertraline has been demonstrated to have one-third the *in vitro* potency for DA reuptake as D-amphetamine (Bolden-Watson and Richelson, 1993).

Zubenko *et al.* (1987) suggested that the mechanism of antidepressant-induced akathisia was by means of enhanced neurotransmission through β-adrenoceptors. This hypothesis was also advanced by Pohl *et al.* (1988) to account for antidepressant-induced jitteriness. Lipinski *et al.* (1989) extended this hypothesis by suggesting that all drugs which powerfully enhanced noradrenergic and/or serotonergic neurotransmission could potentially produce the akathisia jitteriness syndrome by the same net effect: the inhibition of DA neurotransmission in the mesocorticolimbic pathway.

Table 9 Effect of antidepressants on the uptake of biogenic amines *in vitro* (Hyttel, 1993)

Drug	5-Hydroxy-tryptamine	Noradrenaline uptake	Dopamine uptake
Citalopram	1.8	6100	40000
Sertraline	0.19	160	48
Paroxetine	0.29	51	5100
Fluvoxamine	3.8	620	42000
Fluoxetine	6.8	370	5000
Clomipramine	1.5	21	4300
Amitriptyline	39	24	5200
Imipramine	35	14	17000
Nortriptyline	570	3.4	3500
Desipramine	200	0.83	9100
Lofepramine	800	2.7	5300

IC_{50} values. NM: lower values indicate higher potency

Fluoxetine is the least selective amongst the SSRIs for the reuptake inhibition of serotonin relative to NA (Hyttel, 1993; Bolden-Watson and Richelson, 1993). This lack of selectivity of fluoxetine may result in effects on NA reuptake in addition to serotonin. When inhibition of NA uptake by fluoxetine and desipramine was compared using rat cerebral cortex (Harms, 1983; Hughs and Stanford, 1995), it was observed that there was little difference in the potencies of these two compounds. However, this lack of selectivity may be a special feature of the cerebral cortex, because comparisons of the effects of fluoxetine and desipramine on NA uptake in the hippocampus (Bolden-Watson and Richelson, 1993) and hypothalamus (Koe *et al.*, 1983; Thomas *et al.*, 1987), produce differences in the K_i and IC_{50} values in the order of 100–400-fold.

Jordan *et al.* (1994) utilized *in vivo* microdialysis to simultaneously measure serotonin, norepinephrine, and DA in the medial prefrontal cortex of rats receiving imipramine, fluoxetine and fluvoxamine. They found that imipramine and fluoxetine both increased norepinephrine and DA release, while fluvoxamine produced very minimal effects on these two neurotransmitters. Therefore, compared with fluoxetine and imipramine, fluvoxamine had a more selective neurochemical profile *in vivo*. The effects of fluoxetine on extracellular monoamines have been shown to vary over time: acute administration of fluoxetine elevated DA and serotonin concentrations in the rat prefrontal cortex but only serotonin remained elevated after chronic administration (Tanda *et al.*, 1996). Chronic treatment with sertraline increased NA levels in rat prefrontal cortex (Nutt *et al.*, 1997). Citalopram increased NA efflux in the ventral tegmental area at a concentration 100-fold higher than that required to increase serotonin efflux (Chen and Reith, 1994). The administration of citalopram has been shown to decrease extracellular DA concentrations in the striatum (Dewey *et al.*, 1995). The reasons for these effects on extracellular NA and DA concentrations are unresolved. Heteroreceptors (e.g. 5-HT receptors on NA neurone nerve terminals) are a possibility but direct effects on NA and DA reuptake cannot be ruled out.

SSRIs: sigma binding sites

The SSRIs differ in their affinity for the σ-binding site in the brain. Sertraline and fluvoxamine have high, fluoxetine and citalopram have moderate and paroxetine has low affinity for σ_1-binding sites (Tulloch *et al.*, 1995; Narita *et al.*, 1996; Sanchez and Meier, 1997).

The precise role of the σ-binding site in brain functioning is unclear. It is known that σ-binding sites have a high density in many brain regions that control movement (Grundlack *et al.*, 1986 review). Experimental studies have demonstrated that σ_2-ligands dose dependently inhibit the firing of rubral neurons (Matsumoto and Walker, 1992). Faherty *et al.* (1997) studied the effects of single injections of the SSRIs sertraline, paroxetine, citalopram, fluoxetine and fluvoxamine into the red nucleus of the rat and compared the resulting motor disturbances with those elicited by known σ-ligands. The known σ-ligands predictably caused an acute dystonic reaction and torticollis lasting for 5 min following the injection. Of the SSRIs investigated, fluvoxamine and fluoxetine induced moderate dystonia, suggesting that they may produce some of their dystonic effects by acting at σ_2-binding sites. In addition, chronic treatment with fluvoxamine, in contrast to paroxetine, sertraline and citalopram has been shown to augment σ_2-ligand-induced dystonia in rats (C. J. Faherty, A. J. Harkin and B. E. Leonard, unpublished).

Activity at σ-binding sites may also modulate DA function within the brain (Bastianetto, *et al.*, 1995). This modulation of DA function may be due to interaction with N-methyl-D-aspartate (NMDA)-type receptors, which are known to play an important role in the nigrostriatal system (Iyengar *et al.*, 1990). A recent study has suggested a potentiating effect of σ-ligands on NMDA receptor-mediated glutaminergic neurotransmission (Maurice *et al.*, 1994).

SSRIs: 5-HT_{2C} receptors

Fluoxetine has affinity for the $5HT_{2C}$ receptor as suggested in some *in vitro* and *in vivo* studies (Wong, *et al.*, 1991; Jenck *et al.*, 1993; Wood *et al.* 1993; Tulloch *et al.*, 1995; Palvimaki *et al.*, 1996). As discussed in this review, 5-HT_{2C} receptor antagonists have demonstrated their utility in the management of SSRI-induced akathisia. If fluoxetine was a weak 5-HT_{2C} receptor agonist, this activity might augment the potential for fluoxetine to cause side-effects of agitation and/or akathisia. Drugs interacting with 5-HT_{2C} receptors, such as the partial serotonin agonist *m*-chlorophenylpiperazine, the active metabolite of nefazodone and trazodone, have been shown to produce symptoms of anxiety, derealization, stimulation and impaired cognition (Murphy *et al.*, 1989).

SSRIs: CYP2D6

Given the frequent recommendation for long-term antidepressant therapy, an area requiring further study is the potential long-term health consequences of substantially altering cytochrome P450 enzyme function (Preskorn and Magnus, 1994). There is a suggested association between genetically deficient CYP2D6 function and the development of Parkinson's disease (Barbeau *et al.*, 1985), which has found some support in epidemiological studies (Smith *et al.*, 1992). Genetically deficient CYP2D6 functions have been shown to be twice as common in patients with Parkinson's disease as in age-matched controls (Armstrong *et al.*, 1992; Smith *et al.*, 1992). Steiger *et al.* (1992) also found a statistically significant higher incidence of CYP2D6 deficiency in patients with Parkinson's disease vs controls ($p<0.01$). However, these findings have not been confirmed by all investigators in the field (Gudjonsson *et al.*, 1990).

The potential link between deficient CYP2D6 activity and the pathogenesis of Parkinson's disease has been highlighted by the environmental neurotoxin, MPTP (*N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which induces a form of parkinsonism clinically indistinguishable from the common forms of the disease. MPTP is selectively toxic to dopaminergic cells in the substantia nigra and is metabolized by CYP2D6 (Fonne-Pfister *et al.*, 1987).

It has also been suggested that CYP2D6 may be functionally related to the DA transporter (Nisnik *et al.*, 1990; Tyndale *et al.*, 1991; Allard *et al.*, 1994), and that deficient CYP2D6 activity may compromise DA neuronal response to neurotransmitters. CYP2D6 activity status may be a useful marker

of dopaminergic function, independent of its role in metabolizing drugs. For example, EPS and akathisia have been found in poor metabolizers of CYP2D6 substrates to a degree not accounted for by comparatively modest elevations in the plasma levels of their antidopaminergic medication (Brosen, 1990; Llerena *et al.*, 1992). In addition, neuroleptic-induced side-effects such as EPS, tardive dyskinesia and sedation have been shown to have a higher incidence in CYP2D6 poor metabolizers (Pollock, 1995; Armstrong *et al.*, 1997; Andreasson *et al.*, 1997). Significant correlation has been described between the degree of impairment of CYP2D6 activity and the severity of tardive dyskinesia during long-term neuroleptic treatment (Arthur *et al.*, 1995). In most reports of SSRI-induced EPS the CYP2D6 activity status of the patient has not been determined. However, a choreiform syndrome has been reported in a 74-year-old woman with deficient CYP2D6 activity who was receiving fluoxetine (20 mg/day) for the treatment of major depression (Marchioni *et al.*, 1996).

SSRIs: agitation, melancholia and serotonin overstimulation

The emergence of symptoms of akathisia could be mistaken for a worsening of depression, especially the conversion of non-agitated depression to an agitated form. Furthermore, psychomotor agitation present prior to antidepressant therapy may be a risk factor for SSRI-induced akathisia (Adler and Angrist, 1995). Lipinski and colleagues (1989) speculated that agitated depression and fluoxetine [SSRI]-induced akathisia might share the same pathophysiology. Sweet *et al.* (1993) found subjective akathisia type symptoms to be common amongst geriatric patients presenting with major depression. Subjective improvements in dysphoria have usually been noted in patients successfully treated for akathisia (Poyurovsky *et al.*, 1995c).

It has been suggested that fluoxetine is not an appropriate choice of antidepressant for depressed patients with agitation or restlessness (Maany and Dhopesh, 1990). However, the distinction has been made in reference to fluoxetine between agitation and restlessness appearing during treatment and the effects of fluoxetine on depressed patients anxious or agitated prior to the initiation of treatment (Tollefson *et al.*, 1995). The results of the analysis of the patient subgroup with baseline psychomotor agitation in a 6-week double-blind study comparing sertraline and fluoxetine in 284 out-patients with major depression indicate that this may not be a valid distinction (Bisserbe *et al.*, 1996). Fluoxetine demonstrated significantly less efficacy in depressive and anxiety symptoms in the subgroup of patients with psychomotor agitation compared to the sertraline-treatment group. Furthermore, patients with psychomotor agitation at baseline demonstrated a higher incidence of premature treatment discontinuation for side-effects of agitation, anxiety and manic reaction in the fluoxetine group (6.5%) relative to the sertraline group (0%). Furthermore, in a 6-month double-blind study comparing sertraline and fluoxetine in the treatment of 236 depressed out-patients, a significant difference in favour of sertraline was observed on the Hamilton Depression Scale item 9—psychomotor agitation at study endpoint (Sechter and Troy, 1997). In addition, Small *et al.* (1995) re-examined data from a double-blind, placebo controlled study in 671 elderly (> 60 years) out-patients with major depression in a stepwise regression model for potential predictors of treatment response. This analysis indicated that the absence of agitation predicted response to fluoxetine (Fig. 1). In a linear regression analysis of this data by the author to assess the trend for response to decrease with increasing agitation it was significant for fluoxetine ($p<0.01$), but not for placebo ($p<0.05$).

Pindolol, a β-adrenergic and 5-HT$_{1A}$ receptor antagonist, has been reported to improve the response rates to SSRIs in open studies (Artigas *et al.*, 1994; Blier and Bergeron, 1995) and to fluoxetine and paroxetine in placebo-controlled studies (Perez *et al.*, 1997; Tome *et al.*, 1997). The mechanism is thought to relate to antagonism of 5-HT$_{1A}$ receptors. However, is it possible that the β-adrenoceptor antagonist activity of pindolol by decreasing agitation, in a similar manner to the amelioration of symptoms of agitation in akathisia by β-adrenoceptor antagonists, may allow the antidepressant effects of SSRIs, such as fluoxetine, to become manifest.

In the study of Heiligenstein *et al.* (1993) fluoxetine demonstrated significant efficacy vs placebo in the subgroup of depressed out-patients with melancholia. However, fluoxetine was significantly less effective than venlafaxine and nortryptyline in studies of hospitalized depressed patients with melancholia (DeClerc *et al.*, 1994; Roose *et al.*, 1994). Sertraline has shown comparable efficacy to amitriptyline and clomipramine and superior efficacy to mianserin and fluoxetine in outpatients with endogenous or melancholic depression (Reimherr *et al.*, 1990; Malt, 1995; Bisserbe *et al.*, 1996; Latimer *et al.*, 1996; Lepine *et al.*, 1997). Citalopram demonstrated significantly less efficacy relative to clomipramine in hospitalized patients with endogenous depression

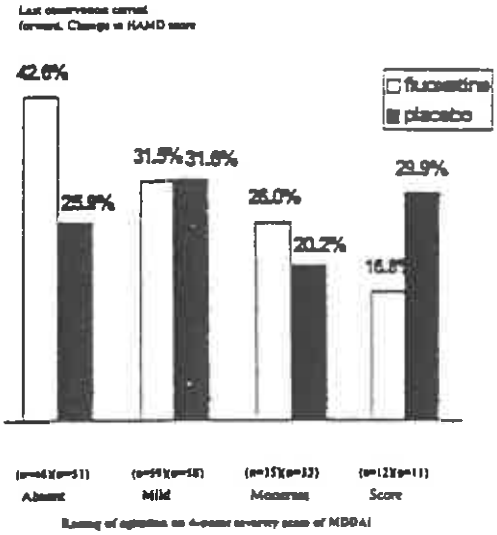

Figure 1 Baseline agitation on item 10 of Major Depression Disorder Diagnostic Assessment Instrument (MDDAI) and response to fluoxetine and placebo in 6-week elderly depression study

(DUAG, 1986) and paroxetine was significantly less effective than imipramine, clomipramine and sertraline in hospitalized patients (DUAG, 1990; Lauritzen *et al.*, 1996; Zanardi *et al.*, 1996).

The product insert for fluoxetine describes 'anxiety, nervousness, and insomnia' in 10 to 15 percent of treated patients, leading to drug discontinuation in 5 percent (Medical Economics Data, 1995). In placebo-controlled studies, fluoxetine has been associated with significantly more side-effects such as insomnia, agitation and anxiety (Small *et al.*, 1995). In a prospective naturalistic study of fluoxetine in 248 general psychiatric out-patients the most common events leading to withdrawal of treatment were anxiety/agitation (4%), headache (2%); insomnia (2%) and aggression (1%) (Mortimore and Blacker, 1996). Mild or subthreshold akathisia may account for these side-effects of fluoxetine. For example, 'the inner sense of restlessness', criterion for the diagnosis of akathisia might be described by the patient or the clinician as anxiety or agitation. Thus, these side-effects may be the milder and more common manifestations of a spectrum of behavioural toxicity at the end of which is overt akathisia.

Comparative clinical studies have shown that sertraline may be associated with fewer of these types of side-effects than fluoxetine (Aguglia *et al.*, 1993; van Moffaert *et al.*, 1995; Bisserbe, *et al.*, 1996). Moreover, in a study of patients discontinuing fluoxetine for side-effects of mainly headache, insomnia, agitation and anxiety who were then treated with sertraline after a suitable wash-out period, sertraline therapy was well tolerated (Brown and Harrison, 1995). In the aforementioned 6-week double-blind comparative study of sertraline and paroxetine in 46 hospitalized depressed patients with psychotic features, the dropout rate in the paroxetine group was substantial (41%) for side effects of anxiety, agitation and insomnia (Zanardi *et al.*, 1996). However, side-effects of agitation, anxiety, insomnia and manic reaction appear to be dose-related (Fabre *et al.*, 1995). The few comparisons between SSRIs to date have used different dosing/titration regimens and have been conducted in varying patient populations. Thus, the relative potential of each SSRI to induce these effects requires more systematic evaluation.

Serotonergic overstimulation and akathisia may be more likely if doses of SSRIs are higher than optimum. Serotonergic overstimulation may be especially disabling if doses are raised in response to an apparent return or worsening of depressive symptoms. Numerous reports document relapse of depressive symptomatology after initial response to SSRIs (Fichtner *et al.*, 1991; Cain, 1992; Rapport and Calabrese, 1993; Goldberg *et al.*, 1995). These patients often further decompensated with dosage increases, and improved markedly when SSRI was discontinued. It has been suggested that the re-emergence of depressive symptoms, particularly anxiety, agitation and dysphoria after initial good response may be the result of serotonergic overstimulation (Bouchard, *et al.*, 1989; Lipinski *et al.*, 1989; Sternbach, 1991), and that this may occur in the absence of typical SSRI side-effects (Cain, 1992).

Unlike the TCAs, in which the optimum dose appears close to maximum tolerated doses, the SSRIs have a relative lack of side-effects that could place their optimum doses well below doses at which side-effects are seen. It has been demonstrated in 6-week fixed dose studies that doses higher than 20 mg/day of fluoxetine or paroxetine and 50 mg/day of sertraline are usually no more effective in the treatment of major depression (Wernicke *et al.*, 1987; Dunner and Dunbar, 1992; Fabre *et al.*, 1995). However, the much longer half-life of fluoxetine means that the use of higher-than-necessary dosages may be almost inevitable. It takes 6–8 weeks for fluoxetine and norfluoxetine to approach steady-state plasma levels (Preskorn *et al.*, 1991; Newhouse *et al.*, 1996). Improvements during the initial 6 weeks on a fixed-dose of fluoxetine may occur before steady-state plasma levels have been achieved.

Thus, 20 mg/day of fluoxetine as a starting dose may result in a relatively higher proportion of patients (eventually) receiving higher-than-necessary plasma levels to achieve or maintain antidepressant response compared to other SSRIs. The insidious rise in plasma levels during the initial 6–8 weeks of treatment with a fixed dose of fluoxetine means that treatment emergent side effects and toxicity can develop late in treatment. Furthermore, the similarity of such events to symptoms of depression can make proper assessments of causation difficult and clinicians and patients may be tempted to escalate dosages resulting in further serotonergic

Table 10 Pharmacokinetic profiles of SSRIs (Lane, 1996b)

Feature	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Elimination half-life	33 h in non-elderly	1–3 days acute; 4–6 days chronic; 4–16 days for norfluoxetine	15 h	21 h at low dose in non-elderly	26 h
Steady-state levels including active metabolite	7–14 days in non-elderly	4–8 weeks	7 days	7 days at low dose	7 days
Clinically relevant SSRI activity of metabolite	No	Yes (norfluoxetine)	No	No	No
Dose increase produce disproportionate increase in plasma levels	No	Yes	Yes	Yes	No
Half-life markedly increased in elderly	Yes	Unknown	No	Yes	No

overstimulation akathisia (Lavin *et al.*, 1993). Thus, the different pharmacokinetic profiles of the SSRIs (including length of half-life, time to achieve steady-state, proportionality of increases in plasma levels to dose increases and the presence or absence of continuing accumulation of a long-acting active metabolite) may be an additional contributing factor to possible variation in the potential to cause akathisia amongst the SSRIs (see Lane, 1996*b* for review; Table 10).

Conclusions

Reports in the literature suggest that SSRI administration may rarely be associated with extrapyramidal reactions. Most likely SSRIs influence DA neuron firing in the substantia nigra through their effects on serotonin input into this nucleus. A direct effect of serotonin via the innervation by serotonergic neurons of primary motor areas, is a possible alternative explanation, especially for dystonic reactions. The rarity of these events suggests that the contribution of an additional factor, namely biological variance between individuals, may be considerable. Predisposing factors such as comorbid Parkinson's disease or concomitant antidopaminergic therapy may increase the likelihood of extrapyramidal reactions or an exacerbation of pre-existing problems. However, this should not preclude the use of SSRIs in depression associated with Parkinson's disease and/or depression and negative symptoms in schizophrenia, where their potentially significant role requires further investigation.

Pharmacodynamic mechanisms have been suggested to explain why enhanced serotonergic neurotransmission may result in extrapyramidal effects. Their more common occurrence in situations of serotonergic hyperstimulation and their response to dose reduction or discontinuation illustrates the importance of pharmacokinetic mechanisms. Furthermore, some of the SSRIs may affect the metabolism of other psychotropic medications. The role of the cytochrome P4502D6 isoenzyme in the brain has yet to be fully elucidated.

It is possible that the relative selectivity of the various SSRIs for serotonin vs DA reuptake inhibition may result in differing potential amongst the SSRIs to cause certain extrapyramidal effects. Paroxetine is the most selective SSRI for serotonin reuptake relative to DA and it has also been reported to be associated with more EPS, such as orofacial dystonia. However, these findings require confirmation before any conclusions may be drawn.

The rare occurrence of akathisia when SSRIs are administered even to patients with predisposing factors, points to the fact that certain individuals may have an underlying constitutional predisposition to these SSRI-induced effects. This is also illustrated by reports of patients who, having previously experienced akathisia when receiving neuroleptics, had a recurrence of akathisia when administered SSRIs. SSRI-induced akathisia is indistinguishable from neuroleptic-induced akathisia except that SSRI-induced akathisia is less common, usually somewhat milder, and symptoms of parkinsonism or dystonia, which invariably accompany neuroleptic-induced akathisia, are often absent. The syndrome of akathisia has not been clearly defined to date and its pathophysiology is far from clear. The subjective components of akathisia are so distinct and overwhelming that it is doubtful whether akathisia should be classified as a motor disorder. It is not yet clear whether the subjective inner restlessness and dysphoria that characterize this condition are sufficient in themselves (i.e. without the objective motoric components), for its diagnosis. Further research is required on the subjective components of akathisia and the subtle affective symptoms heralding motor manifestations.

All SSRIs have the rare potential to cause akathisia. However, 5-HT_2 agonism, lack of selectivity for inhibition of serotonin relative to NA reuptake and potential for accumulation due to a long half-life may increase the risk of akathisia in patients receiving fluoxetine. However, quantification of differences in the potential of individual SSRIs to cause akathisia requires more systematic evaluation.

Increased knowledge of the complex interdependency between dopaminergic and serotonergic systems in brain, and particularly in the basal ganglia have opened new avenues for exploring the pathophysiology and pharmacology of depression and other brain disorders. It is not yet clear how fruitful these new avenues will be. However, they have led to a great increase in the attention given to the neurotransmitters and the neuronal connections of the basal ganglia.

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