1. INTRODUCTION

Movement disorders constitute a group of neurological diagnoses characterized by changes in muscle tone, the presence of inappropriate movements, the impairment in timing and sequencing of normal movements, and the absence of weakness. As a group, these disorders have their origin in disruption of brainstem and subcortical circuits, known as the basal ganglia system, that involves several neurotransmitters, primarily dopamine and acetylcholine, but also serotonin, norepinephrine, gamma amino butyric acid, and glutamate (Jankovic 2003).

Some movement disorders relate to primary neurodegenerative diseases like Parkinson’s disease or various parkinsonism-plus syndromes. In these cases, neurodegeneration occurs in selective, but often multiple brain regions within, and sometimes beyond the basal ganglia system. Other movement disorders are considered as non-degenerative conditions associated with central nervous system neurotransmitter imbalances, like primary dystonia and Gilles de la Tourette syndrome. Still others are clear genetic conditions, like Huntington’s disease and familial tremor.

In addition to these primary movement disorders, similar movement impairments can occur as a reflection of metabolic disturbances, infectious diseases, and cerebrovascular accidents. A final category of secondary movement disorders is composed of the syndromes directly related to medication side effects, collectively termed drug-induced movement disorders. In this latter category, psychiatric medications used to treat psychosis and mood disorders are particularly notable for their associations with movement disorders. Often collectively termed “extrapyramidal symptoms” or “EPS”, these disorders are variable phenomenologically and include tremors, chorea, dystonia, tics, myoclonus, akathisia, chorea and parkinsonism (Gershanik 1993). This chapter focuses on clinical syndromes associated with dopamine-receptor blocking agents

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primarily used to treat psychosis, and agents used in the treatment of mood disorders, specifically antidepressants and lithium carbonate. Because anxiolytics are not associated with movement disorders except during drug withdrawal, they are not discussed. Likewise, drugs that are used in psychiatry but more typically prescribed in other medical arenas or in general medical care, like anticonvulsants or sleeping medications, are not discussed. Each section presents the clinical disorders associated with these psychiatric drugs in terms of phenomenology and temporal development relative to medication exposure. Then, a discussion of data related to biological mechanisms and treatment follows. The final focus concerns available information related to pharmacogenetic research and the search for genetic markers to identify subjects at particular risk for developing movement disorders related to psychotropic medications. Whereas no markers applicable to patient screening have yet been identified, the discussion highlights areas of current research and provides a context for future studies in this domain.

2. MOVEMENT DISORDERS INDUCED BY DOPAMINE RECEPTOR SITE ANTAGONISTS

Numerous movement disorders are associated with the use of drugs that block dopamine receptors. Whereas the majority of such agents are used to treat psychosis, some are predominantly prescribed by internists for nausea, gastrointestinal problems and post-menopausal symptoms (metoclopramide, sulpiride, clebopride, veralipride) (Kompoliti 2003). The agents used for psychosis include phenothiazines, butyro-phenones and other heterocyclic compounds including benzamides and a variety of newer generation antipsychotics, termed “atypical”. Some calcium channel blockers (flunarizine and cinnarizine) and selective serotonin reuptake inhibitors may have some antidopaminergic activity as well. Movement disorders are clinically divided into acute, subacute, and chronic disorders depending on their time of onset relative to medication introduction or dosage increase. Acute dystonic reactions occur within hours, akathisia and parkinsonism within days or weeks, and tardive dyskinesia, in its various forms, after at least three months of chronic therapy. Each disorder has a distinct clinical presentation, biological basis and treatment. Pharmacogenomic data are modest for all these drug-induced movement disorders, but the largest number of studies focus on tardive dyskinesia.

2.1. Acute dystonic reactions

2.1.1. Clinical features

Dystonia refers to a movement disorder typified by tonic contractions of muscles, often with a twisting component. Acute neuroleptic-induced dystonias are seen early in the course of neuro-leptic therapy and are often seen following a single parenteral dose. Dystonic manifestations can be diverse, although the most common clinical signs involve the eyes and neck and are termed “oculogyric crises” (Goetz 2001). Patients complain of inability to move the eyes in the vertical
plane and experience double or blurred vision and discomfort or pain on attempted gaze. Most often, the eyes maintain a sustained upward gaze in association with a retrocollic spasm of the neck, termed “opisthotonos.” Other muscles, including truncal and limb-related, may be involved in acute drug-induced dystonias, especially in children, but these varieties are uncommon among adults. When laryngeal muscles are affected, respiratory stridor can be life threatening (Gershani 2002). Dystonic symptoms persist for hours or days after stopping the causative drug, though clinical intensity of symptoms may wax and wane.

Males develop acute dystonic reactions twice as frequently as females, and children and young adults are the highest group at risk for these reactions. In one series, among young males, aged 30 years or less, over 90% experienced some form of acute dystonic reaction when exposed to neuroleptic drugs (Magnuson 1999). An underlying psychiatric diagnosis of mania was formerly considered a higher risk than schizophrenia, but this difference likely relates to the higher peak doses used in managing acute manic and hypomanic episodes (Khanna 1992). The propensity of a given drug to cause acute dystonic reactions parallels the drug’s associated prevalence of parkinsonism. The piperazine group of neuroleptics has the highest likelihood of precipitating dystonic reactions, and the piperidine (thioridazine) group and newer generation neuroleptics like clozapine have a low propensity. Clinically, the simultaneous administration of anticholinergic agents at the time that dopamine receptor site antagonists are introduced is thought to decrease the risk of neuroleptic-induced dystonia, and the acute administration of anticholinergic agents typically reverses these dystonias (see below).

2.1.2. Biological Basis and Treatment

Because dystonias in other medical contexts are thought to involve primarily the putamen and its output pathways, most of the focus on understanding a biological basis of acute dystonic reactions has been on the dopamine-acetylcholine balance implicit to striatal function and D2 receptor activity. Multiple hypotheses have been offered. Suddenly enhanced dopamine turnover in response to dopamine receptor blockade could theoretically explain this adverse event, but treatment with a dopamine-depleting agent, alpha-methyl-paratyrosine, fails to prevent acute dystonic reactions. These observations, therefore, cast serious doubt on presynaptic dopaminergic release as a primary pathophysiological mechanism (Gershani 2002; McCann 1990). It is also possible that the dopamine receptor blockers induce other neurochemical changes besides cholinergic disruption, for example, secondary involvement of gamma-amino-butyric acid in the putaminal-pallidal pathway and resultant enkaphalin enhancement. In support of this hypothesis, dopamine receptor antagonists with a high likelihood of acute dystonic reactions like piperazine-based neuroleptics also have high binding affinities for sigma-1 and sigma-2 receptors (Matsumoto 2000).

Regardless of these observations, the prevailing concept for the biological basis of acute dystonic reactions from dopamine receptor antagonists is a direct disruption of striatal dopamine-acetylcholine homeostasis. As such, with D2 and possibly some D1 receptors blocked, acetylcholine acts in relative, though not absolute, higher striatal concentrations and precipitates the dystonic behaviors seen.
This theory is supported by a low incidence of acute dystonia with neuroleptic agents with high anticholinergic properties, like thioridazine and clozapine. It is further supported by the reduced risk of acute dystonia when neuroleptics are started with an anticholinergic agent. Finally, years of empiric clinical experience demonstrate that successful treatment of acute dystonias occurs with intravenous or intramuscular injections of a centrally active antimuscarinic agent (trihexyphenidyl) or antihistaminic drugs with anticholinergic properities (diphenhydramine) (Kompoliti 2003). Such treatment usually reverses acute dystonic reactions within minutes. Because these drugs are very short-acting when given intravenously or intramuscularly, oral anticholinergic agents must be prescribed for the next 24 to 48 hours. If the neuroleptic cannot be stopped because of primary psychosis or other reasons, patients must be placed on maintenance anticholinergic treatment for several weeks or switched to another neuroleptic with a lower propensity to cause dystonia. If the dystonic reaction is mild, no intervention is needed and spontaneous resolution should occur if the neuroleptic is stopped. Even if neuroleptic treatment continues in these cases of mild dystonia, usually there is a gradual, spontaneous resolution of dystonic complications after several weeks of continued neuroleptic treatment.

2.1.3. Pharmacogenomics

No studies have established specific molecular biological or genetic attributes of risk for acute dystonic reactions to dopamine receptor antagonists. The repeated reported male predominance of this adverse effect however suggests a possible link to sex chromosomes. Whereas the CYP2D6 genotype or phenotype of poor debrisoquine metabolism can be linked to several acute effects of dopamine receptor antagonists including sedation, postural hypotension and autonomic dysfunction, there is no relationship with risk for acute dystonia (Spina 1992; Armstrong 1997). Because all clinically utilized dopamine antagonists block the D2 receptor system, studies have focused on genetic polymorphisms of this receptor’s gene in patients with and without various movement disorder side effects. A comprehensive survey of nine polymorphisms of the D2 receptor site gene did not identify any genetic marker of acute dystonia (Kaisir 2002).

2.2. Subacute akathisia

2.2.1. Clinical features

Akathisia is a severe, subjective sense of restlessness, often associated with pronounced anxiety that provokes a patient to move incessantly (Gershanik 2002). The movement disorder of akathisia usually involves stereotypic and repetitive pacing, marching or shifting leg movements that are purposefully performed in order to relieve the restless discomfort. The patient may also demonstrate repetitive hand movements, truncal rocking, and panting respirations (Sunami 2000). Unlike dystonias, akathitic side effects of dopamine receptor antagonists develop after days of therapy. Akathisia is not a prominent symptom in most medical or neurological disorders, but it is common in Parkinson’s disease, in iron deficiency syndromes,
and can be seen in cases with structural putaminal of pallidal lesions (Jankovic 2003; Barton 1990).

Neuroleptic-induced akathisia is a frequently unrecognized and therefore likely underreported side effect of therapy. Because psychiatric patients starting neuroleptics are often mentally and motorically agitated, it may be difficult to ascribe new movements properly to drug-induced restlessness. Frequency estimates of akathisia among patients starting neuroleptics or increasing their dose is approximately 33%. The problem can be so distressful that it has been linked to suicide and medication non-compliance (Hirose 2000; Duncan 2000).

The risk for developing akathisia increases as the dose and antipsychotic potency of neuroleptics increase. Newer generation (“atypical”) neuroleptics are not devoid of risk, and risperidone and haloperidol have been reported as having equal propensity for precipitating this adverse effect (Rosebush 1999). Subjects with acute mania may have a higher absolute rate of akathisia than schizophrenics, but this observation is most likely explained by the higher doses used to control the former diagnosis. Though not firmly established, the development of subacute akathisia has been suggested to predict a risk for poor treatment outcome and a higher risk of tardive dyskinesia among schizophrenics (Nair 1999; Eichhammer 2000).

2.2.2. Biological basis and treatment

The biological basis of dopamine receptor antagonist-induced akathisia is poorly understood, but the occurrence of akathisia in other conditions suggests some clues. The frequent association of drug-induced parkinsonism with akathisia and the spontaneous occurrence of akathisia in Parkinson’s disease itself suggest that the nigro-striatal dopaminergic system plays a direct role. Cases with structural subcortical lesions associated with akathisia have most damage in the putamen or outflow tracts to the globus pallidus. Because the movements are predominantly leg stereotypies, subcortical-spinal networks or mesocortical pathways are likely involved. Whereas traditionally, D2 dopaminergic receptor blockade was hypothesized to be at the core of akathisia, this disorder has a less predictable pharmacology than acute dystonia. Noradrenergic and opioid influences play a likely role in the pathophysiology, because beta-noradrenergic blockers and opioid antagonists are sometimes effective therapies if the neuroleptic cannot be withdrawn (Kompoliti 2003). These secondary chemical influences likely involve brainstem nuclei or mesospinal pathways. Serotonergic/dopaminergic imbalance has also been suggested to play a role in akathisia, based on evidence that some of the newly developed neuroleptics with high affinity for 5HT3 receptors have a low index of akathisia (Hirsch 2002). The link of akathisia to iron metabolism has been studied, and at least in some studies, neuroleptic-treated patients with and without akathisia have both lower iron and lower ferritin plasma levels than healthy controls (Kugol 2003). Those with akathisia tend to have lower levels than non-akathic subjects, but the iron and ferritin levels still fall within the normal range (Hofmann 2000). Though iron levels influence dopamine D1 and D2 receptor numbers and sensitivity in rats, exact cellular effects caused by dopamine receptor antagonists in humans have not been identified (Erikson 2001).
The anguish experienced by patients with akathisia prompts the need for clinicians to diagnose and treat this condition immediately. Withdrawal of dopamine receptor antagonists will abate symptoms over days. Lowering the dose can also be adequate or a switch to a more low potency neuroleptic may resolve the problem without sacrificing necessary control of psychosis. In the event that these solutions are not successful, the clinician enters into the realm of vague empiricism, and agents that have been used cross several pharmacological systems. Decreasing noradrenergic activity with beta-blockers, like propranolol, or with low dose clonidine that is thought to act to downregulate noradrenergic systems through autoagonism at presynaptic receptors have been used with success in some series of patients (Gershmanik 1993). Opioid antagonists like propoxyphene may be effective, and some serotonin receptor antagonists, specifically those preferentially blocking 5HT2 receptors like mianserin, are reported to abate akathisia in subjects on neuroleptics (Poyurovsky 1999). Recent reports that ziprasidone, has a very low propensity to provoke akathisia and yet is effective in managing psychotic agitation provides additional evidence that serotonergicblockade may be beneficial in avoiding neuroleptic-induced akathisia (Hirsch 2002). Finally, it is important to determine if the patient has both akathisia and drug-induced parkinsonism with tremor, rigidity and bradykinesia, because in these cases, amantadine or anticholinergic agents may treat both syndromes (Gershmanik 1993).

2.2.3. Pharmacogenomics

Because all clinically used antipsychotic agents have activity one the D2 dopaminergic receptor system, genetic variants that might modulate therapeutic and adverse effect profiles have been examined. In the comprehensive survey of nine known polymorphisms of the D2 dopamine receptor cited above, no genetic pattern could detect subjects with akathisia. As will be discussed further in the section on tardive dyskinesia, particular emphasis has been placed on the dopamine D3 receptor gene in regards to side effects of dopamine receptor antagonists. Subjects whose alleles are homozygous for the Ser9Gly polymorphism of this gene are twice as likely to develop akathisia as subjects with other polymorphisms (Eichhammer 2000). This same pattern has been reported in several studies of tardive dyskinesia (see below), suggesting a molecular biological link between the two conditions and reinforcing clinical observations that akathisia is a predictor of tardive dyskinesia risk. 19,20 No relationship has been established between CYP2D6 polymorphisms or phenotype of debrisoquine metabolic patterns and akathisia (Dahl 2002; Andreassen 1997).

2.3. Subacute parkinsonism

2.3.1. Clinical features

Days or weeks after starting or increasing the daily dose of dopamine receptor antagonists, patients may experience the gradual development of bradykinesia, rigidity, gait, and balance instability and resting tremor. When these signs appear in unison, the diagnosis of parkinsonism is not difficult, but often the early signs are
subtle with more vague symptoms of increasing slowness and difficulty with movement (Kompoliti 2003). In these cases where tremor is not prominent, the clinician, family, and patient may misinterpret drug-induced parkinsonism as a global overmedication effect or as a sign of impending depression, especially in subjects with bipolar affective disorders. The signs of drug-induced parkinsonism are not different from Parkinson’s disease itself, although the latter is usually dominated by less symmetric signs. Tremor is seen when the patient’s hands are relaxed in the lap, and the movement disorder abates as the patient moves and executes tasks of daily living (resting tremor). Fine motor movements like buttoning, opening envelopes, manipulating an eating utensil become slow and difficult, although there is no weakness (bradykinesia). On examination, while the patient remains relaxed, the clinician can detect hypertonicity with a ratchet-like quality (cogwheel rigidity). Difficulties rising from a chair, initiating walking, pivoting smoothly to turn, and resisting a postural threat, usually tested by pulling abruptly on the shoulders to assess if patients can right themselves without falling backwards, all are indicative of gait and postural reflex impairment. All signs may be present simultaneously, but often the syndrome only partially develops, so that the physician must be sensitive to all clinical features. Elderly patients are thought to be at higher risk for this side effect than younger patients, but there is no established gender predominance. Particularly characteristic of drug-induced parkinsonism is rest tremor that predominates in the lips and chin, provoking a rhythmic flutter that has been termed “rabbit syndrome” (Meltzer 1987). The movement disorder is a parkinsonian tremor and must be differentiated from the more choreic lingual buccal movements of tardive dyskinesia (see below).

2.3.2. Biochemical basis and treatment.

Because Parkinson’s disease and drug-induced parkinsonism are phenotypically indistinguishable, similar biochemical bases for the two disorders have been proposed (Kawans 1973). In Parkinson’s disease, the primary degenerative lesion is loss of the dopaminergic cells projecting from the pars compacta of the substantia nigra in the mesencephalon to the putamen and caudate nucleus (striatum). These cells interact primarily with D2 receptors (Jankovic 2003). The primary site of action for neuroleptics precipitating drug-induced parkinsonism is this same post-synaptic dopamine D2 receptor population within the striatum. Patients with preclinical Parkinson’s disease may be at a high risk for drug-induced parkinsonism. One case series identified patients referred for evaluation of neuroleptic-induced parkinsonism (Goetz 1983). Although the parkinsonism resolved over months after neuroleptic withdrawal, patients returned within three years with idiopathic Parkinson’s disease. The treatment of drug-induced parkinsonism preferably includes cessation of the provoking agent, but in the case where neuroleptic continuation is needed, anticholinergic drugs or amantadine can be useful (Gershank 2002). Because neuroleptic metabolism often involves the generation of several intermediate or end products with dopamine antagonist properties, full drug clearance should be not be presumed until three or four months after cessation.
2.3.3. Pharmacogenomics

The phenotypic similarity between Parkinson’s disease and dopamine receptor antagonist-induced parkinsonism has prompted researchers to posit hypotheses that may relate the two at a molecular biological level. None of these has proved fruitful at the present time. A number of hereditary forms of familial parkinsonism have been identified and these include abnormalities located on chromosomes 1p, 2p, 4q, 5q, 6q, 8p, 9q, and 17q (DeStefano 2002; West 2002). Defects in pathways involved in intracellular proteolysis or energy metabolism unify these forms of familial parkinsonism. Though these defects are not seen in most cases of non-familial Parkinson’s disease, they give clues to the areas of focus for future studies and have not been specifically studied in relation to drug-induced parkinsonism. Testing of polymorphism patterns among subjects with drug-induced parkinsonism may reveal risk factors shared by both disorders. Early reports of links between young-onset Parkinson’s disease and P450 metabolism, though later not confirmed, led to searches for different patterns of CYP2D6 polymorphism among subjects with drug-induced parkinsonism. Like the studies in Parkinson’s disease, there have been inconsistent results: Several, though not all, show a significant increase or trend towards overrepresentation of mutated CYP2D6 alleles among subjects who develop dopamine receptor antagonist-induced parkinsonism (Lane 1997; Pollock 1995; Arthur 1995).

These studies are methodologically imperfect, and in some series, subjects were taking antipsychotic agents not specifically metabolized by the P450 system or were on multiple drugs with different mechanisms of action. Based on studies of the genetics of Parkinson’s disease, polymorphism patterns for several other genes are reasonable research targets, including manganese superoxide dismutase gene, the E2 subunit of the alpha-ketoglutarate complex, the alpha-1-antichymostatin gene, monoamine oxidase B intron 13, and the catechol-O-methyl transferase gene (Kruger 2000; Mizuta 2000; Goudreau 2002).

2.4. Tardive dyskinesia

2.4.1. Clinical features.

Tardive dyskinesia is a general term that describes movement disorders specifically provoked by chronic exposure to dopamine receptor antagonists (Kompoliti 2003). In a more restrictive context, some authors refer to this entity as “tardive syndrome”, reserving tardive dyskinesia to connote the typical lingual-facial-buccal distribution and choreic phenomenology of the most classic form of this dyskinesia (Gershanik 2002). The rapid and repetitive movements include lip smacking, tongue darting, and chewing movements that are unsightly and disruptive to social interactions, dental hygiene, and vocal communication (Joseph 1999). When the diaphragmatic muscles and vocal apparatus are involved, irregular gasping respirations and noises may also occur. Other non-choreic forms of tardive dyskinesia include tardive dystonia, generally typified by back arching and retrocollic neck postures (Burke 1982), tardive tics or repetitive stereotypic eye blinks, facial grimaces and sometimes more complex movements (Klawans 1982),
tardive myoclonus typified by lightning-like jerks (Tominaga 1987), and even tardive tremor (Stacy 1992). In all cases, tardive dyskinesia relates to chronic exposure to dopamine receptor antagonists and should not be diagnosed in the context of recent introduction (less than three months) of medication, after recent increases of medication dosage, or as a spontaneously developing disorder without medication exposure.

It is not clear why some patients develop one tardive syndrome and others develop another. In most instances, however, at least mild lingual-facial-buccal movements are present even when there are more prominent dystonic, tic, or myoclonic features. In fact, from a clinical perspective, the combination of multiple phenomenologies within the same patient should suggest the diagnosis of tardive dyskinesia (Kompoliti 2003).

The time of onset and context of development for tardive dyskinesia are variable. By definition, the exposure time to drug must be a minimum of three months, and the risk appears to increase with exposure duration and cumulative dose. Other proposed risk factors have been age and gender, with elderly women usually being considered the subjects at highest risk. These data are based on estimates that approximately 5% of exposed young adults develop tardive syndromes, whereas in patients over 45, the rate exceeds 30%, and in older institutionalized subjects the prevalence is 60% (Byne 1998). Within the elderly population, a reduced rate of dyskinesia occurs in very old subjects, an observation that be explained by documented late age-related loss of striatal dopamine receptors (Sweet 1992). Overall, an estimated 15-20% risk occurs (Koshino 1992). Often tardive dyskinesia first appears at a time when the clinician is lowering the overall medication dosage (withdrawal dyskinesia). It can also, however, first occur on steady doses (breakthrough dyskinesia). Because many cases are short-lived, especially among children who usually experience rapid and spontaneous remission, these cases are rarely even counted among the tardive dyskinesia statistics.

For adults, however, once tardive dyskinesia develops, it is likely that some form of movement disorder will persist. Some remain stable, but some become more intense over time even if the causative medication is stopped (Crane 1971; Koshino 1991). Remission rates vary depending on the follow-up observation time, and it is clear that some cases resolve as late as five years after cessation of the causative drug (Gershaniuk 2002).

The choice of neuroleptic drug is likely important to the risk of tardive dyskinesia. Although not extensively studied with carefully controlled trials, traditional neuroleptics of the piperazine group and the butyrophenone, haloperidol, are thought to have the highest risk of causing tardive dyskinesia, followed by the piperidine compounds, like chlorpromazine, and lastly by the piperidine neuroleptics, like thioridazine and the newer generation compounds, including clozapine, olanzapine, quetiapine, ziprasidone, and aripiprazole. Even with these latter agents, however, a risk of tardive dyskinesia is present, and risk is thought to be dose and duration related (Glazer 1993).

Besides high neuroleptic dosing, concomitant use of anticholinergic medications has also been implicated as a clinical risk factor. This issue is particularly important, because it is entirely physician controllable and, in many countries, neuroleptic medications are introduced with automatic co-prescriptions of
anticholinergics. Whereas short-term, this type of treatment is likely useful for preventing or minimizing drug-induced acute dystonias, chronic treatment with anticholinergics may not only be unnecessary, but may be promoting a potentially irreversible side effect (Muscettola 1993). Another treatment strategy in managing psychiatric illnesses has been intermittent attempts at “drug holidays” or short, medication-free periods, but one study suggested that neuroleptic interruptions were associated with a threefold increase in tardive dyskinesia risk (Van Harten 1998).

2.4.2. Biological basis and treatment

Several explanations have been posited to explain the underlying pathophysiology of tardive dyskinesia. A primary theory has long focused on neuroleptic-induced receptor site hypersensitivity caused by chronic receptor blockade (Klawans 1973). In this way, secondary increases in dopamine turnover occur in dopamine cells projecting to the chemically denervated structures. According to this model, when the dopamine receptor antagonist dose is reduced or the drug withdrawn, dopamine acting at hypersensitive receptors would provoke the various hyperkinetic movement disorders typical of tardive dyskinesia. Each phenomenological variant of tardive dyskinesia could correspond to a different hypersensitized neuroanatomical area, for instance, the striatum for chorea, the putaminal-pallidal system for dystonia, and the mesocortical projections for tics.

This traditional concept has been challenged because the predominant phenomenologies of tardive dyskinesia are not drug-specific and every drug can cause all types of movement disorders. More extensive understanding of the basal ganglionic circuitry has also allowed more extensive analyses of neurotransmitter systems that may be directly or indirectly implicated in the biological basis of tardive dyskinesia. In this light, greater emphasis has been placed on the subthalamic nucleus, because it is known to be an important integrative center in basal ganglionic function, and alterations in its activity influence signs of parkinsonism, chorea, dystonia and other movement disorders. Chronic neuroleptic use causes loss of gamma-aminobutyric acid-mediated inhibition from this nucleus that normally regulates thalamic activation of the cortex. Unchecked thalamo-cortical activity could theoretically cause a wide variety of movement disorders affecting descending cortico-spinal, cortico-brainstem, and especially cortico-subcortical networks (Mitchell 1992). Excessive activation of thalamo-cortical function primarily involves the neurotransmitter glutamate, and tardive dyskinesia has also been suggested to relate to excitotoxic effects of glutamate and related compounds (Naidu 2001). A complementary hypothesis focuses on the opioid system, because animals treated with chronic neuroleptics have reduced activity of the medial globus pallidus, ventral anterior and ventral lateral thalamic nuclei, as well as markedly increased subcortical metenkephalin levels. Drugs associated with low frequencies of tardive dyskinesia, like clozapine, do not induce metenkephalin-like immunoreactivity responses whereas a more traditional neuroleptic, haloperidol, causes significant enhancement (Auchus 1992). Other neurotransmitters and neuromodulators studied in models of tardive dyskinesia include neurotensin because its striatal concentration increases after chronic neuroleptic exposure, and cellular energy markers such as cAMP, cGMP and nitric
oxide levels, because their levels decrease in anatomical regions with supersensitive D2 receptors (Bester 2000).

New interest has focused on neuroleptic effects on D1 receptors, those linked to adenyl cyclase enzymatic activity. Whereas typical neuroleptics primary block D2 receptors, leaving D1 variably affected, high turnover rates of dopamine consequent to the D2 receptor blockade could abnormally activate D1 receptors. In an animal model of tardive dyskinesia, rats with genetically mediated inactivated D1 receptor expression developed fewer abnormal movements when treated with chronic neuroleptics than those with full D1 function (Van Kampen 2000). The D3 receptor system, important to the antipsychotic efficacy of management of psychosis, has been studied in terms of genetic polymorphisms that might affect the risk of developing tardive dyskinesias among subjects exposed to dopamine receptor antagonists. (See below).

Based on these multidimensional theories, a single therapeutic target for the treatment of tardive dyskinesia has not been established. Because the dopamine antagonists are the causative agents, these drugs should only be used when needed. By definition, the disorder occurs in subjects exposed to at least 3 months of therapy, so short-term treatment can potentially eliminate risk. If involuntary movements develop, withdrawal or reduction in dose may lead to a transient increase in intensity, but over time movements stabilize or improve in most patients. In some patients, however, tardive dyskinesia can increase in intensity and spread to new body regions even after full withdrawal of medications. In patients who need to remain on dopamine antagonists for primary psychiatric or medical disease, switching to agents associated with a lower perceived risk of tardive dyskinesia, clozapine, quetiapine, risperidone, olanzapine, ziprasidone, aripiprazole can be effected.

Dopamine-depleting drugs, like reserpine and tetrabenazine have been used with some success in treating tardive dyskinesia, but these agents are associated with drug-induced parkinsonism and depression, so they may not be feasible treatments. Very low dopamine agonists, felt to activate dopaminergic presynaptic autoreceptors and thereby decrease dopamine release have been advocated from small observational studies. Calcium channel blockers and GM1 ganglioside, aimed at promoting neuronal repair, have been used, as well as vitamin E, but results have not been consistent enough to advocate wide usage (Lerner 2001).

In terms of treating individual movement disorders, because the most frequent manifestation of tardive dyskinesia is choreic or stereotypic and repetitive, anticholinergics should generally be slowly withdrawn and stopped if possible. For cases of marked tardive dystonia, anticholinergic agents may be symptomatically helpful for the tonic spasms, though the faster, clonic movements of other phenomena may increase.

In severe cases, neurosurgical procedures to target the globus pallidus or subthalamic nucleus may be warranted.

2.4.3. Pharmacogenomics

CYP2D6 polymorphisms have been examined in relation to tardive dyskinesia, but there is no consistent relationship (Dahl 2002). Other reports suggest that an
intronic polymorphism in the CYP1A2 gene may contribute to tardive dyskinesias risk, but these studies have not involved large numbers of subjects (Ozdemir 2001). Nine polymorphisms of the D2 dopamine receptor have been examined in a series of over 600 schizophrenic patients and no relationship with tardive dyskinesias has been established with any of them (Steen 1997). In regards to the D3 system that is felt to be related to psychotic and some locomotor behaviors, mutations in genes related to the D3 dopamine receptor itself have been examined. In several studies, including a combined analysis of 780 patients, Ser9Gly polymorphism has been associated with increased risk for tardive dyskinesia (Steen 1997; Basile 1999; Segman 1999). Other studies, however, have failed to reproduce these observations (Reitschel 2000). When an association is found, the increased risk conferred by the D3 polymorphism is independent of age and gender (Segman 2000). Even if the association exists, the positive predictive value of D3 receptor glycine alleles for tardive dyskinesia, is quite low, and therefore testing of subjects prior to neuroleptic exposure has no real practical utility at the present time. In China, where tardive dyskinesia is reported to be infrequent, no association between this polymorphism and tardive dyskinesia has been found (Garcia-Barcelo 2001). Other genes that have been associated with an increased risk of tardive dyskinesia in at least one report include the 5HT2C receptor gene (Segman 2000), 5HT2A receptor gene (Segman 2001), and the manganese superoxide dismutase gene (Hori 2000). Given the complexity of phenotypic expressions of tardive dyskinesias, it is feasible to search for gene interactions or additive gene contributions. An additive effect between the D3 polymorphisms and the 5HT2C receptor gene profile has been reported to influence severity of abnormal involuntary movements in one analysis, though no statistical interaction was documented (Segman 2000). The same team suggested an interaction between the Ser9Gly polymorphism of the D3 receptor and the cytochrome P450 17-alpha-hydroxylase gene (CYP-17) in determining tardive dyskinesia severity. They found CYP-17 allelic status to influence subjects homologous for the glycine allele of the D3 receptor gene (Segman 2002). Clearly such observations require confirmation by independent groups, but with developing technological tools and large patient cohorts already identified, testing can be performed with efficiency. Smaller studies have subdivided patients with tardive dyskinesias by phenomenological presentation and focused on tardive dystonia only, but without finding relationships to the cytochrome P450 enzyme or to polymorphisms of the D2 receptor (Taq1A and -141C Ins/Del) or the D3 receptor (Ser9Gly) (Mihara 2002).

3. TRICYCLIC ANTIDEPRESSANTS

3.1. Tremor and myoclonus

3.1.1. Clinical features

Subjects treated with amitriptyline, imipramine and other tricyclic compounds can develop a fine, rapid postural tremor that is maximally apparent when the patient holds his hands out or tries to execute a task. This movement disorder may
occur in as high as 10% of exposed subjects (Kompoliti 2003). Fine motor control is impaired because of the shaking, and typically handwriting is jerky or the subject spills food when trying to use a soup spoon or other utensil to transport food from the plate to the mouth. Occasionally more rapid and high amplitude jerks, termed myoclonus, can develop, and this movement is more disabling. Tremors can occur in the context of normal cognitive function, but when myoclonus occurs with tricyclic drugs, it is usually part of a generalized delirium, indicative of acute or sub-acute drug intoxication.

3.1.2. Biological basis and treatment

Postural tremors are generally believed to relate to high noradrenergic activity in subcortical pathways, possibly also involving inputs from the cerebellum to the ventral-anterior and ventral-lateral nuclei of the thalamus. The known blockade of noradrenergic presynaptic reuptake that is inherent to tricyclic antipressant activity is considered the origin of tricyclic-related tremor. Myoclonus, on the other hand, is generally linked to serotonergic dysfunction, and in different clinical settings, both over- and under-activity of serotonergic systems can be associated with myoclonus. In the case of tricyclic antidepressant overdose, myoclonus is presumed to relate to heightened serotonergic activation at reticular-spinal, and reticular-subcortical and reticulo-cortical systems. The serotonergic reuptake mechanism of tricyclic antidepressants is thought to play at least a partial pathophysiological role in tricyclic-induced myoclonus, but anticholinergic intoxication and a more generalized encephalopathy unlinked to a single neurotransmitter has also been suggested. Based on these observations, treatment involves the cessation of tricyclic drugs, hydration, and in the case of severe myoclonus, physical protection from self-injury. Resolution of tremor and myoclonus is anticipated shortly after drug cessation. In cases where these signs occur in the context of suicide attempts, reversal of toxic signs including the movement disorder, can be hastened by giving cholinesterase inhibitors aimed at reversing anticholinergic intoxication.

3.1.3. Pharmacogenomics

Because the field of pharmacogenomics is more modern than the era of wide usage of tricyclic compounds, these agents have not been studied extensively in relation to genetic markers of efficacy and no study has focused on movement disorder side effects. Because chronic administration of tricyclic compounds results in down regulation of the 5HT2 receptor, individual patient genetic profiles for the 5HT2 receptor may be a reasonable target for studying relative risks of myoclonus (Glennon 1995). CPY2D6 polymorphisms have been studied in relation to tricyclic efficacy, but without a specific focus on drug-induced movement disorders (Bertilsson 1997; Lerer 2002). One study examined whether antidepressant-induced myoclonus was associated with CYP2D6 or CYP2C19 polymorphisms reflective of poor psychotropic drug metabolism. The study sample was small and comprised of cases exposed to numerous antidepressants and not just tricyclics. Myoclonus, however, was not associated with a slow metabolizing P450 enzyme
system (Spigset 1997). Other studies have considered an overrepresentation of slow metabolizer-related genotypes of the P450 enzyme system among antidepressant-treated patients and movement disorders, but these case series have a wide variety of drug exposures, different types of antidepressants, and often concomitant neuroleptic exposure (Vandel 1999 and 2000).

3.2. Other reported movement disorders

There are rare reports of chorea, choreoathetosis, and akathisia in association with tricyclic compounds, but the documentation is sketchy and the clinical characteristics poorly characterized. If such conditions developed, treatment would involve withdrawal of the antidepressant. In subjects with long-term treatment with neuroleptics, a concern that the anticholinergic properties of tricyclics could increase the risk of tardive dyskinesia or unveil latent dyskinesia has not been extensively studied. No pharmacogenetic studies are available for these types of movement disorders, though one study compared a group of patients who developed a variety of complications including dystonia, parkinsonism, chorea, and akathisia while on neuroleptics and/or antidepressants. They compared CYP2D6 polymorphisms in the movement disorder group with similarly exposed cases without movement disorders and found a more frequent representation of poor metabolizers in those with movement disorders. The multiple drugs of different mechanisms of action and the multiple movement disorders described makes this report difficult to interpret specifically in the context of tricyclic antidepressants (Vandel 2000).

4. SELECTIVE SEROTONERGIC RE-UPTAKE INHIBITORS (SSRIs)

4.1. Movement disorders

4.1.1. Clinical features

Whereas SSRIs are frequently associated with a vague sense of nervousness, akathisia has also been reported as a specific neurological syndrome of restlessness accompanied by volitional movements, usually, legs and trunk, that are performed by the subject in order to abate the restless feelings. Drug-induced parkinsonism or exacerbation of parkinsonism in patients with Parkinson’s disease has been reported in small series of patients receiving SSRI treatment, but the frequency of such adverse effects has not been studied in detail and some reports found parkinsonian bradykinesia improved with SSRIs (No Authors Listed, Extrapyramidal effects of SSRI antidepressants 2001; Vand de Vijver 2002: Rampello 2002). Acute dystonic reactions when SSRIs are introduced or when the daily dose is increased have been rarely reported in association with SSRI treatment. Myoclonus can occur as well and develop in isolation or in the context of the “serotonin syndrome”, characterized by high fever, myoclonus, rigidity, agitation, autonomic instability and a high risk of rhabdomyolysis and death.
(Charbone 2000). In a review of 127 published reports of SSRI-associated movement disorders, Gerber and Lynd documented 30 cases of akathisia, 25 of parkinsonism, and 19 of dystonia (Gerber 1998). Additionally, 12 cases, termed dyskinesias, six cases of tardive dyskinesia and 15 with “mixed” movement disorders were cataloged, although their characterization was less clear. These investigators also emphasized the possibility of bruxism developing in the context of SSRI-treatment, although whether this complication represented a form of dystonia is difficult to ascertain from the clinical descriptions.

4.1.2. Biological basis and treatment

SSRI-related movement disorders are felt to relate either to enhanced serotonergic activity (myoclonus) or to indirect effects on other amine systems, specifically dopaminergic. Electrophysiological and biochemical evidence suggest that serotonergic neurons in the raphe nucleus inhibit dopaminergic neurons in the substantia nigra (Dray 1976). Furthermore, large doses of fluoxetine inhibit dopaminergic synthesis (Baldessarini 1990). These effects could underlie aggravated parkinsonism, acute dystonia, and akathisia, conditions usually associated with hypodopaminergic states. To treat all movement disorders induced by SSRI’s lower doses or discontinuation will resolve the clinical problem.

4.1.3. Pharmacogenomics

As with other drugs, the main pharmacogenetic focus has been the P450 metabolic pathways and genetic determinants of rapid and slow drug metabolizers. None of the SSRI-associated extrapyramidal side effects has yet to be associated with specific genotypes (Vandel 1996). Because SSRIs inhibit cytochrome P450, blood levels of drugs that are substrates for this enzyme system would be expected to rise during SSRI treatment. Such drugs include both tricyclic antidepressants and monoamine oxidase inhibitors. A specific search for allelic patterns related to CYP2D6 would be reasonable. Because of the clinical reports that Parkinson’s disease can be exacerbated by SSRI’s in some patients (No Authors Listed, Extrapyramidal effects of SSRI antidepressants 2001; Van de Vijver 2002), focused genetic studies on biomarkers currently identified to be associated with some forms of genetic Parkinson’s disease would be reasonable to test in SSRI-sensitive subjects. No specific studies have examined serotonergic or dopaminergic receptor polymorphisms among subjects with SSRI-related movement disorders.

5. LITHIUM CARBONATE

5.1. Movement disorders

5.1.1. Clinical features

Two specific movement disorders of clinical importance are associated with lithium treatment, a fine postural tremor seen when patients have normal therapeutic
drug levels and a course irregular tremor, often associated with myoclonus that is seen with toxic levels of the drug (Gershanik 1993). In the former case, the tremor is small amplitude with the characteristics of enhanced physiological tremor, occurring with the hands outstretched or when the subjects tries to stabilize the extremity during eating or writing. Typically patients spill soup when bringing the hand to the lips or tremble as they write. When plasma levels of lithium increase beyond the therapeutic range, the tremor becomes large amplitude and disruptive of all coordinated activities. Often, superimposed lightning-like myoclonic jerks cause abrupt movements and can cause sudden spilling of food or even dropping of objects. Dyssnergy and ataxia with poor coordination and stumbling gait can also occur, and these movement disorders may be accompanied by loss of consciousness and seizures (Kompoliti 2003).

Lithium treatment has been occasionally reported to exacerbate Parkinson’s disease, though the validity of this claim is suspect in several instances (Lecamwasam 1994). Most reports of this effect document enhanced tremor, but parkinsonian tremor is generally a rest-predominant tremor and distinct from the postural tremor associated with lithium. Because some Parkinson’s disease patients have postural tremor as part of their clinical disorder, the lithium tremor should not be considered in itself an exacerbation of parkinsonism. Convincing reports of actual changes in bradykinesia, as distinct from ataxia, enhanced rigidity, and postural reflex impairment increases outside of the context of ataxia are not well-established.

5.1.2. Biological basis and treatment.

The neurochemical basis of tremorgenic effects due to lithium carbonate is not completely understood. Most agents that cause or exacerbate postural tremors predominantly affect the central noradrenergic system, and it has been largely presumed that effects on the cerebellar outflow system or the motor integration paths leading to the ventrolateral and ventroanterior thalamic areas are responsible for lithium-induced tremors (Kompoliti 2003). Whereas the two tremor syndromes are clinically distinct, there is likely a common mechanism for both, the latter syndrome representing a more severe noradrenergic disruption than the former. Because lithium carbonate is a simple salt compound, ion channels are likely the subcellular site of action, and more than one neurotransmitter system may be involved. Treatment involves cessation of the drug or lowering of daily dose. Drugs typically used to abate postural tremor, like β-noradrenergic antagonists, can provoke depression and must be used with caution. Primidone and the antidepressant, mirtazapine, also can abate postural tremor.

5.1.3. Pharmacogenomics

No studies have examined genotypes of subjects receiving lithium therapy to determine risk factors for postural tremor or the toxic tremor/ataxia syndrome. Because patients who need lithium therapy are most commonly afflicted with bipolar affective disorder, they represent significant clinical challenges for drug compliance and dosage management. If subjects at risk could be identified,
enhanced vigilance and more frequent monitoring could be appropriately incorporated into their clinical care. Because lithium treatment regularly involves patients providing blood samples for medication monitoring, these same samples, if accompanied with clinical data on the presence or absence of tremor, could be easily used to develop a large bank of material for pharmacogenetic studies.

6. FUTURE PERSPECTIVES

The traditional clinical separation between neurology and psychiatry has impeded progress in the study of drug-related movement disorders. Multispeciality groups of psychiatrists, neurologists, pharmacologists and molecular biologists are well-positioned to develop programs that break down this traditional separation and will potentially address pivotal scientific questions of clinical import. These questions include: which subjects are likely to develop movement disorders when exposed to various medications to treat underlying psychiatric diseases?: is the risk of specific movement disorders related to certain genotypes?: is the risk related to or independent of the genetic risk factors for the underlying psychiatric illness?: is the risk of one type of drug-induced movement disorder more genetically linked than others?: is the risk of drug-induced movement disorders linked to the genetic markers of the same phenomenology seen in conditions unrelated to drug exposures (e.g., is drug-induced parkinsonism related to genetic risk factors for Parkinson’s disease)?

The goal of such research is the identification of subjects likely to develop drug-induced movement disorders prior to their exposure and thereby avoid these disorders as common adverse effects of therapy. In concert with similar research efforts to identify the factors that accurately predict efficacy of psychotropic treatments, clinicians and patients may look forward to the selection of a single best treatment that is both safe and rationally chosen to have maximal benefit. This goal remains unrealized at the present time, but the research outlined in this chapter demonstrates the concerted focus on moving from conceptual frameworks to practical application. Because very large sample sizes are needed for this area of research, enhanced government, foundation, and pharmaceutical sponsorship as well as concerted collaborations between large teams of clinical and laboratory scientists will be essential to the achieve the needed advances in pharmacogenetics.

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