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A Review of the Pathophysiology of Psychological Disorders in Persons with Parkinson's Disease

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Abstract
Assisting patients to quit smoking continues to be critical for all health care providers as the Surgeon General's report in 2004 reported a significant increase in the number of diseases caused by smoking. Awareness of the extreme addictiveness of nicotine may help health care providers increase empathy for patients attempting to quit. Health care providers can identify the patient's stage of change, according to the Transtheoretical Model, and incorporate appropriate pharmacological and educational methods to aid in the quit attempt.

Introduction
Parkinson's disease (PD) is a neurodegenerative disorder affecting between 18 and 418 per 100,000 people worldwide (Schrag, 2002), and between 750,000 to one million people in North America (Weiner, Schulman, & Lang, 2001, p. 20). While the precise etiology of the disease is unknown, numerous factors have been implicated as potentially causative. Although the neurodegenerative nature of the disease supports a biological basis for psychological distress, the functional impairments and tremendous personal and financial costs infer that at least a component of psychological distress in PD is due to environmental factors.

From a clinical perspective, hallmark symptoms of PD include resting tremor, rigidity, bradykinesia, and loss of postural reflexes (Starkstein & Merello, 2002, p. 7). Tremor is typically the first symptom of the disease, and generally manifests in the hands, lower lip, chin, and less often in the legs, as the inhibitory, or extrapyramidal, motor system becomes more dysfunctional. In contrast, rigidity is characterized by resistance to passive movement and feelings of stiffness. The symptom of bradykinesia refers to a slowness or impaired initiation of movement, and "loss of postural reflexes" refers to difficulty standing from a sitting position, maintaining balance when standing, problems standing upright, and spontaneous loss of balance (Starkstein & Merello, et al., p. 7). In addition to the aforementioned physical symptoms, research has shown that numerous psychological disorders may manifest in those with PD, either as a result of the disease, in reaction to the disease, or as side effects of pharmacological treatments of the disease.

An understanding of the etiology and maintaining factors of psychological disorders is essential for effective treatment. Some have proposed a biological etiology to psychiatric disorders in PD, (Mayeux, Stern, Williams, Sano, & Cote, 1986; Tandberg, Larsen, Aarsland, Laake, & Cummings, 1997; Chow, Masterman, & Cummings 2002), though others have posited that psychiatric disorders, such as depression, as being an emotional reaction to the disease (Bieliauskas, Klawans, & Glantz, 1986; Bieliauskas & Glantz, 1989). Limited but promising research has shown nonpharmacological interventions to be beneficial to

persons with PD (Gauthier, Dalziel, & Gauthier, 1987; Westbrook & McKibben, 1989; Mohr et al., 1996; Dreisig, Beckman, Wermuth, Skovlund, & Bech, 1999; Pacchetti et al., 2000; Heinrichs, Hoffman, & Hofmann, 2001, Kenney & Kelleher, 2003). Nonetheless, it is essential for mental health professionals to recognize and incorporate possible physiological etiologies of psychological distress into case conceptualization and treatment.

Psychological Disturbance in PD: An Epidemiological Review

While some psychological disturbances in persons with PD may be parallel to the functional impairments as well as biochemical imbalances associated with the disease, other disturbances may be secondary to pharmacological treatment of the disease. Disturbances such as depression, anxiety, dementia, and apathy, appear to be more disease than treatment related, while psychosis and delusions are most commonly observed as possible side effects of pharmacotherapy. The epidemiology of these disorders shall be further reviewed below.

The most common psychological problem observed in the PD population is depression (Menza, 2002). Epidemiological reports of depression in PD have ranged from 7% to 90% (Starkstein & Merello, 2002, p. 94), though many studies cite an approximate 40-50% range (Murray, 1996; Tandberg, et al., 1997; Hoogenduk, Sommer, Tissingh, Deeg, & Wolters, 1998; Erdal, 2001).

Starkstein and Merello (2002, p. 122) reviewed literature of anxiety in persons with PD and reported that anxiety disorders may be observed in an estimated 30-50% of cross-sectional samples. Other authors also report a high incidence of anxiety disorders among PD patients, however they report the most commonly encountered are panic disorder, generalized anxiety disorder, and social phobia (Marsh, 2003).

Dementia, distinguished by cognitive deficits characterized by impairment of learning or memory, including impaired language, praxis, object recognition or executive functioning, has also been observed in persons with PD. In a review of studies estimating the prevalence of dementia, Marder and Jacobs (2002) found estimates ranging from 8% to 93%, with more up-to-date studies suggesting an approximate 20 to 40% range.

Apathy, characterized by diminished motivation, emotional responsiveness and goal directed behavior, has also been observed in the PD population (Schulman, 2002). In one study of 50 patients, 12% showed apathy, while 30% were both apathetic and depressed (Starkstein et al., 1992).

Nearly one half of persons on medication management for PD will have behavioral or psychiatric side effects to their medications (Weiner et al., 2001, p. 153). Neuropsychological side effects of antiparkinsonian medications, particularly dopaminergic therapy, include vivid dreams and nightmares, hallucinations, delusions, paranoia, and disorientation (Weiner et al., p. 153). Other more rare non-psychotic disorders associated with dopaminergic medication therapy include mania, hypomania, and changes in sexual behavior and sexual satisfaction (Molho, 2002).

In summary, PD segues into both biological and psychological symptomatology. To understand the pathophysiology of PD, it is first necessary to understand those mechanisms of the brain in which PD manifests. A discussion of the basal ganglia and its role in motor control/inhibition, and as a dopamine producing/dependent region of the brain is crucial to this understanding. Numerous basal ganglia physiology models exist, with many commonalities (Young & Penney, 2002). This paper shall briefly review a simplified basal ganglia model, with emphasis on the model proposed by Stewart (2001)

Basal Ganglia

The basal ganglia is a group of interconnected nuclei located beneath the cerebral cortex; it is integral in controlling motor and cognitive functions (Young & Penney, 2002), and is also involved with motor learning, sequencing, movements, attention, and memory (Ring & Serra-Mestress, 2002). Involved in an extremely complex network of feedback loops, the basal ganglia mainly receives signals from and sends signals back to the cortex. Particularly, the basal ganglia exerts control on the ventrolateral thalamus, which consists of numerous nuclei, and has an excitatory output to the motor cortex for initiating movement (Stewart, 2001).

The structures of the basal ganglia include the striatum, consisting of the putamen and caudate. The striatum is one of the main entries for information entering the basal ganglia (Wichmann, Smith, & Vitek, 2002) from the neocortex (perception of objects), hippocampus (learning and memory), amygdala (emotions and fear response) and olfactory cortex (Starkstein & Merello, 2002,

pp. 16-17; Rosenzweig, Leiman, & Breedlove, 1999). The putamen receives inputs from the frontal association cortex, and the caudate receives input from the sensorimotor cortical zones (Rosenzweig, et al., p. 304).

The globus pallidus interna (GPi) and substansia nigra pars reticula (SNr) are the output relay stations of the basal ganglia, connecting to and inhibiting the ventrolateral thalamus, thus inhibiting movement (Stewart, 2001). The GPi receives input from the putamen through direct and indirect pathways. Brown and Mardsen (1998, p. 1801) described the direct pathway as a connection between the putamen and GPi and SNr, and the indirect pathway as involving connections between the subthalamic nucleus (STN), globus pallidus (GPe), GPi, and SNr.

According to Stewart (2001), the direct putamen-GPi pathway is inhibitory on the GPi, meaning this inhibits the "braking" effect of the GPi on the ventrolateral thalamus, allowing the ventrolateral thalamus to initiate movement. Stewart further states that the indirect pathway has an excitatory effect on the GPi, increasing its inhibitory effect on the ventrolateral thalamus, hence decreasing movement.

In summary, the direct pathway decreases the inhibitory effect of the GPi on the ventrolateral thalamus allowing for excitatory stimulation of the motor cortex, which then initiates movement. The indirect pathway increases the inhibitory effect of the GPi on the ventrolateral thalamus, thus having an inhibitory effect on the motor cortex and thus inhibiting movement.

According to Stewart (2001), the substansia nigra is the dopamine (DA) producing region of the basal ganglia, and DA release from this region acts on the direct and indirect pathways, which in turn act on the ventrolateral thalamus. Dopamine 1 receptor stimulation is inhibitory on the direct pathway; therefore, the GPi decreases its inhibitory effect on the ventrolateral thalamus, allowing motor cortex innervation. Stewart further states that dopamine 2 receptor stimulation inhibits the indirect pathway, decreasing the GPi's inhibitory effect, therefore allowing stimulation of the ventrolateral thalamus.

Manifestation of PD

PD is a disease in which the substansia nigra deteriorates, and symptoms do not become manifest until approximately 80% of the substansia nigra has deteriorated (Weiner et al., 2001, p. 7). While neuronal loss in the dopaminergic substansia nigra is primarily implicated in PD (Elble, 2000), other areas, such as the dorsal motor nucleus of the vagus, and the noradrenergic locus coeruleus (Weiner et al., p. 7), thalamus, hypothalamus, cholinergic nucleus basalis of Meynert, dopaminergic neurons of the ventral tegmentum, seratonergic raphe nuclei (Stewart, 2001) also sustain cell loss. According to Stewart, decreased DA release from the substansia nigra disrupts D1 and D2 receptor based pathways (direct and indirect), affecting their ability to moderate motor movement and decreasing excitatory output to the motor cortex from the ventrolateral thalamus.

In summary, the degeneration of the substansia nigra leads to a decrease of DA production, inhibiting stimulation of the direct and indirect basal ganglia pathways, which in turn leads to a decrease of the ventrolateral thalamus' excitatory effects on the motor cortex, resulting in an involuntary decrease in motor function. This involuntary decrease in motor function is evidenced in the aforementioned PD symptoms of tremor, rigidity, bradykinesia, and postural instability. To better understand the manifestation of PD, proposed etiologies of PD are reviewed.

Pathophysiology of PD

A diagnosis of PD requires depigmentation and neuronal loss in the substansia nigra, and the presence of inclusions called Lewy bodies, made of the protein alpha-synuclein (Starkstein & Merello, 2002, p. 14). The role of Lewy bodies in PD has not been precisely determined, and while Lewy bodies are observed in other neurological disorders, PD is a disease in which Lewy bodies are consistently observed (Stewart 2001, p. 16). The precise etiology of PD has not been determined, though numerous factors have been implicated and shall be reviewed.

Tanner (2002) reviewed studies investigating the etiologies of PD. Studies of parkinsonism, or PD-like symptoms, found the drug 1-methyl-4-phenyl-, 1,2,3,6-tetrahydropyridine (MPTP) caused neuronal damage and symptoms very similar to PD, and exposure to certain metals, rural living, farming, gardening, and pesticide use has been implicated as contributing to PD pathophysiology, particularly given the structural resemblance of certain agricultural chemicals to MPTP. Furthermore, Tanner found that PD is more likely diagnosed in older adults, is slightly more common in men than women, and while studies comparing monozygotic to dizygotic twin pairs yield no strong evidence of genetic factors, family studies revealed that first-degree relatives of PD probands were significantly more likely to be diagnosed than relatives of controls. In a more recent study, Lloyd et al. (2003) found that both in utero and adult exposure to cocaine changed MPTP sensitivity in mice from resistant to sensitive, raising questions about the role of cocaine and narcotic exposure as an adult or in utero in PD susceptibility.

While numerous factors have been implicated in the etiology of PD, medication management of these symptoms also plays a crucial role. Given that antiparkinsonian medications may enhance quality of life given their impact on symptom management, such medications may also complicate the person's mental state. A review of these drugs and how they work is essential for an understanding of the manifestation of PD, as well as many of the debilitating psychiatric side effects of these medications.

Medication Management of PD

Numerous medications are used to treat PD symptoms; however, this paper will review three of the most prominent drugs that are often used in combination: Sinemet, Comtan, and Mirapex.

Sinemet is a combination of two ingredients, levadopa and carbidopa. Levadopa is a neutral amino acid originally supplied to the body through foods such as fava beans or in the amino acid tyrosine, and is converted into DA by the enzyme dopa-decarboxylase, which is present in the stomach, liver, kidneys, blood vessels, and brain (Lieberman, 2002). Lieberman further states that if levadopa is solely administered, 99% is converted in the body, and 1% is digested in the cells of the substansia nigra, therefore increased levels of DA throughout the body result in the side effect of nausea.

Carbidopa blocks the dopa-decarboxylase enzyme peripherally, yet does not cross the blood-brain barrier, allowing nearly 10% of a dose of levadopa to enter the brain (Lieberman, 2002). Furthermore, the combination of carbidopa with levadopa has allowed for doses of levadopa to be reduced by about 75%, which has helped reduce side-effects (Silverman, 1998, pp. 1010-1011).

Mirapex is a drug which resembles DA activity at the DA receptor, and may be used in combination with Sinemet or by itself (Weiner et al., 2001, p. 166). Lieberman (2002, p. 230) states that while 50% of people with PD may be maintained on such an agonist with little or no Sinemet, the remainder require additional Sinemet or Sinemet and Comtan.

Catechol-O-methyl-transferase (COMT) is an enzyme found in the liver, kidney, and in lesser amounts in the heart, lungs, and skeletal muscles (Lieberman, 2002). Because COMT is an enzyme which metabolizes DA, a COMT inhibitor such as Comtan was approved by the Food and Drug Administration as an adjunct to levodopa/carbidopa therapy to block the COMT enzyme and increase the availability of DA (Henney, 1999).

Possible Psychiatric Manifestations

As noted, many factors have been implicated in the pathophysiology of PD and the physical manifestations of the disease; however, understanding the possible physiological etiologies of psychological distress in those with PD has also posed a challenge to researchers. While the functional impairments and tremendous personal and financial costs infer that a component of psychological distress in persons with PD is explained by an emotional response to the disease and/or environmental factors, the neurodegenerative nature of PD also supports a biological basis for psychological distress. To facilitate the integration of physiological factors into case conceptualization, pathophysiological mechanisms implicated in psychological distress in persons with PD are reviewed, specifically regarding the constructs of depression, anxiety, dementia, apathy, as well as neuropsychological side effects of antiparkinsonian medications.

Depression

Of the psychological disorders observed in persons with PD, depression is one of the most rigorously investigated. A chapter by Chow et al. (2002) summarized research regarding the neurophysiological and chemical bases of depression in persons with PD, reviewing neuropathological, biochemical, and cerebrospinal fluid studies of DA, serotonin (5-HT), and norepinephrine (NE).

A loss of dopaminergic neurons in the ventral tegmented area has been observed in persons with comorbid PD and depression. Starkstein and Merello (2002, p. 109-110) identify the ventral tegmented area as being an important dopaminergic efferent to limbic and limbic-related brain structures. Furthermore, Chow et al. (2002) identified reduced levels of DA in the mesolimbic pathway as a suspected etiology of depression in persons with PD.

Serotonin (5-HT) is a generally inhibitory chemical located in numerous nuclei of the brain stem, and involved in mood, anxiety, and sleep induction (Seeley, Stevens, & Tate 2002). A review by Chow et al. (2002) indicates that seratonergic neuronal damage is observed in persons with PD, and implicates neuronal loss in the rostral brainstem cell groups and lower levels of the 5-HT metabolite 5-HIAA in cerebrospinal fluid as suggestive of a seratonergenic component to depression in PD. Furthermore, the dorsal raphe nuclei, located in the midline of the brainstem, is the region from which the most prominent seratonergenic pathway emerges (Rosenzweig, et al., 1999, p. 85). Therefore, the more severe neuronal loss in the dorsal raphe observed in

depressed patients with PD versus non-depressed patients with PD (Litvan, Cummings, & Mega, 1998), the observation of reduced raphe echogenicity in the depressed persons with PD (Becker, et al., 1997), and reduced levels of CSF-5HIAA observed in depressed persons with PD (Mayeux et al., 1986) support a seratonergic component to depression in persons with PD.

NE is a neurotransmitter located in small sized nuclei of the brainstem, such as the locus coeruleus, and nerve tracts of NE extend to areas of the brain, spinal cord, and in some autonomic nervous system synapses. NE acts in both an excitatory and inhibitory capacities (Seeley et al., 2003). Neuronal loss in the locus coeruleus accompanies depression in PD, and bradyphrenia has been shown to be positively correlated with reduced levels of NE metabolite (Chow et al., 2002).

Further supportive of a biological component to depression in persons with PD is the effectiveness of medication therapy. A survey conducted by Richard, Kurlan and the Parkinson Study Group (1997) estimated that 26% of patients with PD are on medication therapy for depression, and that physicians used selective serotonin reuptake inhibitors (SSRI's) 51% of the time as the first option, followed by tricyclics 41% of the time, and other agents 8% of the time. Monoamine-oxidase inhibitors are also used for treatment of depression (Hindle, 2001).

Tricyclic antidepressants (TCAs) have been demonstrated as efficacious in reducing depressive symptoms in persons with PD (Poewe & Luginger, 1999). Because TCAs are generally noradrenergic and serotonergic stimulants, with some TCAs having dopaminergic qualities (Chow et al., 2002. p. 150), the effectiveness of such pharmacotherapy supports the hypotheses that a component of depression is proportionate to NE, 5-HT, and DA deficiencies.

While literature of the efficacy of SSRI therapy is less clear, this class of antidepressants has likewise been suggested as helpful in PD depression (Poewe & Luginger, 1999; Samii, Nutt, & Ransom, 2004). Given that these drugs increase 5-HT levels in the brain, resulting in the down-regulation of 5-HT receptors, the helpfulness of these drugs in alleviating depressive symptoms supports the notion that 5-HT deficiency appears to have some association with depression.

Monoamine oxidase is an enzyme that breaks down 5-HT, NE, and DA, therefore, monoamine oxidase inhibitors (MAO-Is) block this enzyme and increase the availability of these amines to the brain (Rosenzweig, et al., 1999, p. 450). Two types of MAO-Is are MAO-I type A (nonselective), which inhibits the breakdown of NE and 5-HT, and MAO-I type B (selective), which inhibits the breakdown of DA (Starkstein & Merello, 2002, p. 144). In discussing the MAO-I type B medication selegiline, Playfer (2001, p. 291) indicates that antidepressant effects are obtained, though not to the extent as those obtained with MAO-I type A inhibitors. While there is concern about CNS toxicity when selegeline is combined with other antidepressant medications (Richard & Kurlan, 1997), the antidepressive effect of MAO-Is further support deficiencies in 5-HT, NE, and DA as biological bases of depression in persons with PD.

Anxiety

Most anxiety disorders are associated with an underlying depressed mood, and it has been suggested that anxiety and depression may have a common mechanism (Starkstein & Merello, 2002, pp. 123-124). Among reviewed proposed mechanisms for anxiety disorders in persons with PD, Marsh (2000) stated that reduced levels of DA may result in disinhibition of the locus coeruleus, an area in which there is a high DA/NE ratio. Anxiety may result from the consequential DA/NE imbalance in the locus coeruleus, a region of the brain that projects to many areas of the cerebellum, cerebrum and spinal cord, and modulates many behavioral and physiological processes (Rosenzweig, et al., 1999, p. 85).

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter, and most neurons of the central nervous system have GABA receptors (Seeley et al., 2003). In a chapter reviewing anxiety in persons with PD, Richard and Kurlan (2002, p. 166) indicated that research has found increased and decreased concentrations of GABA in specific brain regions. Furthermore, positive responses among persons with anxiety disorders to benzodiazepines, which activate GABA receptors in the brain, support the hypothesis that GABA plays a role in anxiety (Richard et al., 2002). In recognition of the scarcity of research regarding medication management of anxiety in persons with PD, Marsh (2000) suggested antidepressant medication as likely effective treatment.

Dementia

Starkstein and Merello (2002, p. 80) reviewed the plausible neuropathological basis of PD dementia, including coexisting Alzheimer's disease (AD), presence of Lewy bodies, dopaminergic neuron depletion, and depletion of cholinergic, NE and 5-HT neurons. Marder and Jacobs (2002) reviewed literature on dementia in PD, citing that in one sample of persons with PD and dementia, coexisting AD was found in 29%, and dementia with Lewy bodies in 10%. The authors further stated that in general, neuronal loss in the locus coeruleus, dorsal raphe nucleus, and nucleus basalis of Meynert has been observed in the brains of

those with PD dementia. Furthermore, PET scans studies have revealed greater hypometabolism in temporoparietal regions compared to nondemented persons with PD.

Despite these findings, no single etiology for dementia has been discovered, and no medications exist for treating cognitive impairment in persons with PD (Marder & Jacobs, 2002). Marder and Jacobs et al. further state that most often, cognitive impairment is addressed by withdrawing medications that possibly worsen such symptomatology (p. 132). Excessive amounts of dopaminergic medications are among those that may induce hallucinations and delusions that can exacerbate preexisting dementia (Samii et al., 2004).

Apathy

Apathy may understandably be reactionary to the disease, though biological mechanisms have also been implicated. The nucleus accumbens, ventral pallidum, and ventral tegmental area have been identified as part of the brain's "motivational circuitry" that receives limbic system input and makes connections with the basal ganglia, a region compromised by PD (Schulman 2002). Dubois and Pillon (2002) also posit the limbic ventral striatopallidal system as integral in motivation and action, and implicate the ventral tegmental area's role with the mesolimbic and mesocortical dopaminergic systems. Apathy has also been observed in patients with corticobasal degeneration (Litvan et al., 1998), and as a side effect of dopamine-blocking medications in persons with schizophrenia (Wyatt, Apud, & Potkin, 1996).

Medication Side Effects

Side effects of medications used to treat PD, particularly those which increase levels of DA in the brain or combinations of drugs such as such as DA receptor agonists, COMT inhibitors, selegiline, and anticholnergics, may produce side effects including vivid dreams and nightmares, hallucinations, delusions, paranoia, disorientation (Weiner et al., 2001, p. 153). Fénelon, Mahieux, Huon & Ziégler (2000) found that visual hallucinations were more common in persons with PD than auditory hallucinations, and emphasized that cognitive impairment, daytime somnolence, and duration of disease were predictive factors of hallucinations.

An observed connection exists between PD and schizophrenia that supports the role of DA in hallucinations; that persons with PD may experience hallucinations when taking dopaminergic medications, and persons with schizophrenia may experience parkinsonian symptoms when taking a DA antagonist such as chlorpromazine (Rosenzweig et al., 1999, p. 445). Connelly (2002) also identified the locus coeruleus as the "dream center" of the brain, and specifically implicated overstimulation of this region in nightmares. Molho (2002) reviewed literature of psychosis in PD, stating that chronic exposure to DA agonists may cause hypersensitivity of DA receptors, as opposed to the expected down-regulation, explaining why such side effects may occur after prolonged use. Interestingly, one study by Makoff et al. (2000) suggested a possible genetic component for drug induced hallucinations in persons with PD involving D2 receptor genes.

Modest reductions in antiparkinsonian medications are usually sufficient to alleviate symptoms of drug-induced psychosis, and reduction of bedtime dosage may be effective in relieving nightmares (Connelly, 2002). A further step is to administer clozapine, a drug which produces D2 as well as 5-HT2 receptor blockade (Meltzer, 1989) and is the only antipsychotic to this date shown to reduce drug-induced psychosis without worsening parkinsonism (Molho, 2002). Molho further speculated that, in treating drug-induced psychosis in persons with PD, antagonistic agents for DA receptors in the mesolimbic pathway, while simultaneously sparing the nigrostriatal pathway, would be ideal in controlling dopaminergic receptor hypersensitivity.

In summary, while an increase in DA in the nigrostriatal pathway may alleviate physical symptoms of PD, elevations of DA in other areas of the brain, particularly the mesolimbic pathway, may result in psychotic symptoms. Medication reduction or concurrent use of clozapine may alleviate these symptoms, and genetic susceptibility to late-onset drug induced hallucinations has been investigated with intriguing results.

Discussion

Understanding of the physiological, environmental, behavioral, and genetic manifestations and maintenance of both biological and psychological disturbances continues to develop as essential components of training for healthcare practitioners working with persons with PD. As interdisciplinary collaboration in healthcare continues to evolve, an appreciation of the dynamic causes, interactions, and manifestations of illnesses such as PD demands a reciprocal complexity and cooperation in the delivery of care. Therefore, it is proposed that a biopsychosocial model in the context of multidisciplinary healthcare appears to be the optimal approach in treating these patients. It is hoped that this paper contributes to an understanding of the obstacles psychological disturbances present in the lives of those persevering through PD and other such illnesses.

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