Depression and anxiety in Parkinson’s disease and Multiple system atrophy

Consequences for treatment

Ida Bang Strand
Veileder: Christofer Lundqvist, professor/overlede

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Abstract

Objective: Parkinson’s disease (PD) is a chronic progressive neurodegenerative disorder characterized by a loss of dopaminergic neurons in the substantia nigra. Hence, the patients suffer from a dopamine deficiency and this causes the cardinal motor symptoms in PD; bradykinesia, tremor and rigidity. Lately, research has shown that also non-motor symptoms play a major role in PD. Among them are depression and anxiety. Multiple system atrophy (MSA) is a rare, neurodegenerative disorder characterized by poor levodopa responsive parkinsonism, extrapyramidal signs, cerebellar ataxia and autonomic failure in any combination. MSA and PD are both classified as alpha-synucleinopathies due to accumulation of this protein in CNS. Similar to PD, non-motor symptoms as depression and anxiety also seems to be present in MSA. This study compares depression and anxiety in MSA and PD to evaluate the consequences for treatment.

A non-systematic search was executed in PUBMED and relevant reviews were included in this study.

Results: There is little research on this topic and very few RCTs addressing anxiety and depression in MSA or PD. However, of the existing material, there is more research done on the PD group than on the MSA group.

For treating depression in PD, SSRIs are most commonly used. However, TCAs have in some studies been found superior to the SSRIs. Other studies found no greater effect of antidepressants than placebo. Recently dopamine agonists have been suggested as another treatment option, but the evidence was found to be insufficient. Rotigotine, a transdermal dopamine agonist patch, recently was included as a treatment option and may improve depression. Also Mirtazepin (an antidepressant) and Bupropion (norepineprine and dopamine reuptake inhibitor) are two new medications that may have effect, but there is not enough research so far to conclude on this.

As for anxiety in PD, benzodiazepines are often used and are found to have some effect. However, due to side effects and possible dependence, this medication should be used with care. Buspirone (a partial 5-HT agonist) may have effect, but there is a lack of RCTs studying this. SSRIs and SNRIs are also used for treating anxiety, but there are no RCTs addressing the use of this medication on anxiety only and therefore insufficient data on this. TCAs were found to be effective, but once again there is the same issue with lack of RCTs. The drug Mirtazepin is also mentioned as a treatment for anxiety, but there is no significant evidence backing this information either. Last, electroconvulsive treatment may also work in drug-resistant anxiety.

In the MSA group, very little literature exists, but psychotherapy, SSRIs and levodopa are mentioned as possible treatments. Alternative treatments listed are electroconvulsive therapy and repetitive transcranial magnetic stimulation.

Cognitive behavioural therapy is found to be efficient in both anxiety and depression in the PD group. There is no literature on this in the MSA group.

Conclusion: As a consequence of low number of studies and a lack of large RCTs addressing the treatment options of anxiety and depression in MSA and PD, practical management is currently based on empirical evidence only. There is insufficient evidence to recommend any treatment for depression and anxiety in the PD and MSA groups. More clinical studies are needed.
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1 Introduction

1.1 Definition of Parkinson’s disease and multiple system atrophy

1.1.1 Parkinson’s disease (PD)

Idiopathic Parkinson’s Disease was first described in 1817 by the English physician James Parkinson in “an essay on the shaking palsy”. (Parkinson 1817) Parkinson’s disease (PD) is a chronically neurodegenerative disease, affecting between 100 and 200 per 100.000 people over 40 years old (Marras C 2004). While PD has traditionally been considered a motor system disorder, it is now recognized to be a complex disease including neuropsychiatric and other non motor features in addition to the motor symptoms (Langston 2006).

The cardinal features of PD are bradykinesia, tremor and rigidity. Postural instability is also included by some, but because it usually appears later in the course of the disease it is not included in any published diagnostic criteria for PD (Gelb DJ 1999). As the diagnostic criteria tell, the diagnosis is based on clinical appearance and generally requires a good clinician to make an early diagnosis.

Parkinson’s disease results from a loss of dopaminergic neurons in the substantia nigra of the basal ganglia. The basal ganglia, also referred to as the extrapyramidal system, include the substantia nigra (SN), striatum, globus pallidus, subthalamic nucleus and thalamus. Patients with PD will develop a dopamine deficiency in the nigrostriatal pathway which causes hypersensitivity of D1 and D2 receptors (Bamford NS 2004). The cardinal symptoms of PD are believed to be caused by dopamine deficiency.

In PD, a reduction of dopamine-producing neurons from the normal complement of approximately 550,000 to 100,000 lead to dopamine depletion in the SN and in the nigrostriatal pathway. Pathologically the brains of the patients with PD is characterized by depigmentation, neuronal loss and gliosis, particularly in the substantia nigra pars compacta (Jankovic 2016). In addition to this Parkinson’s disease also is classified as an alpha-synucleinopathy, due to a dysregulating of the alpha-synuclein protein, among with dementia with Lewy Bodies and multiple system atrophy to mention some. Alpha-synuclein is a protein that accounts for one percent of the total protein in CNS. However, its physiologically role is not fully understood (Vekrellis K 2011).
1.1.2 Multiple System Atrophy (MSA)

Multiple System Atrophy (MSA) is an adult-onset neurodegenerative disease. Prevalence is about 4 per 100,000. Typically age at onset is 53-55 and onset before age 30 has never been reported (Wenning GK 2013). Clinically, it is characterized by a varying degree of levodopa-unresponsive parkinsonism, cerebellar ataxia and autonomic failure (M. F. S. Gilman 2008). Neuropathologically, MSA is characterized by the presence of distinct glial cytoplasmic inclusions (GCIs) formed by fibrillar alpha-synuclein proteins in oligondendrial cells (Papp 1989). Pathologically, this classify MSA as an alpha-synucleinopathy together with Parkinson’s disease, dementia with Lewy Bodies and pure autonomic failure (Spillantini 2016).

Historically, the term multiple system atrophy (MSA) was introduced by Graham and Oppenheimer in 1969 (Graham JG 1969) and included the following three diseases with overlapping pathology: olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND) and Shy-Drager syndrome (SDS). Twenty years later MSA was distinguished into two motoric subgroups, the MSA-OPCA with predominantly cerebellar ataxia and the MSA-SND with predominantly parkinsonism (Quinn 1989). Then, in 1994 Schulz et al. reclassified the MSA-SND as MSA-P and the MSA-OPCA as MSA-C and this are the subtypes still used today (Schulz JB 1994).

As for the MSA diagnosis, the diagnostic criteria have been formed during the last twenty years, starting with Quinn et al in 1989 (Quinn 1989). He formed a base for the clinical consensus criteria presented in 1998/99 (L. N.-S. S. Gilman 1999) and then revised in 2008 (M. F. S. Gilman 2008). The revised clinical consensus criteria put the MSA diagnosis into three levels: probable, possible and definite MSA. Definite MSA require autopsy confirmation, while probable and possible MSA are based on history and physical examination.

Probable MSA is defined as a sporadic, progressive, adult (>30 years)-onset disease. It is characterized by autonomic failure involving urinary incontinence with erectile dysfunction in males or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic. In addition to this, the patient also needs to have poorly levodopa-responsive parkinsonism (bradykinesia, rigidity, tremor or postural instability) or a cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) (M. F. S. Gilman 2008).

Possible MSA is characterized by either parkinsonism or a cerebellar syndrome and at least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA). In addition to this one feature suggestive of MSA is required (M. F. S. Gilman 2008).
1.2 **Definition of depression and anxiety**

1.2.1 **Depression**

Depression is characterized by a depressed mood and a loss of interest or pleasure, following the DSM-V classification (Table 1). These symptoms need to present for at least 2 weeks and present a change from previous functioning (Miquel Baquero 2015) (American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed., (DSM-5) 2013).

<table>
<thead>
<tr>
<th>Table 1 Criteria for major depressive episode: DSM 5</th>
</tr>
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<tbody>
<tr>
<td>Five (or more) of the following symptoms have been present during the same 2-wk period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood; or (2) loss of interest or pleasure</td>
</tr>
<tr>
<td>Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)</td>
</tr>
<tr>
<td>Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day Insomnia or hypersomnia nearly every day</td>
</tr>
<tr>
<td>Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) Fatigue or loss of energy nearly every day</td>
</tr>
<tr>
<td>Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide</td>
</tr>
<tr>
<td>The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)</td>
</tr>
</tbody>
</table>

1.2.2 **Anxiety**

Anxiety is a group of disorders characterized by features of fear and anxiety and related behavioural disturbances. Anxiety is divided into different disorders, such as generalised anxiety disorder, social anxiety disorder, specific phobia, social anxiety disorder, panic disorder, panic attacks and others. The anxiety disorders differ from developmentally normal fear by being excessive and by being persistent for typically over 6 months. The clinician decides whether the anxiety or fear is out of proportion, taking cultural context into account (American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed., (DSM-5) 2013).
2 Methods

2.1.1 Search strategy

The relevant articles used in this study was found by searching the PUBMED database. The strategy used was:
1. Parkinson’s disease OR Multiple system atrophy (16570)
2. Anxiety OR depression (48034)
3. 1 and 2 (1440)

Following filters were added: review, publication date from 01.01.1999 up to today, and English language. Then, 1028 articles were found. By reading through the titles and the abstracts, relevant articles were included. All articles containing patient groups with dementia were automatically excluded from this study. When reading the reviews, relevant primary sources and relevant studies were found and then included in the study.
3 Depression and anxiety in PD and MSA

3.1 Depression in PD
Depression is one of the most common non motor symptoms in Parkinson’s disease. The prevalence of depression in PD wary across studies, raging from 2.7% to more than 90%. A systematic review of prevalence studies of depression in PD showed that clinically significant depressive signs were present in 35% of the patients. (Reijnders JS 2008) Therefore, some state that depression is one of the main factors impacting quality of life in PD patients.

The onset of depression can occur at any time, even precede the motor symptoms (Ishihara 2006) of PD in up to 30% of the patients (Santamaria J 1986). A recent review by Sauerbier et al 2016, puts non motor symptoms in PD patients into different subgroups based on the clinical expression. The theory behind this subgrouping is based on theories suggesting that non-dopaminergic areas in the brainstem may be affected and involved ahead of dopaminergic involvement, more specifically starting in the olfactory bulb and thereafter going through the limbic or brainstem areas. If this is the case, this would lead to dominant expression of NMS over motor symptoms. One of the subgroups is the “Park depression/anxiety” group. This phenotype might occur in late and early onset PD with both depression and anxiety. As Sauerbier et al writes, it is important to consider the symptoms in the context of motor fluctuations. Three different subtypes: anxious depressed, depressed and anxious, have been described. The anxious depressed subtype usually occurs at a younger age and have an early age of onset. The depressed subtype develops at an older age and have a late age of onset, whereas the anxious subtype starts a a younger age and have an early age of onset (Sauerbier 2016).

The pathophysiology of depression in PD is not fully understood. Decreased CSF 5-hydroxyindooacetic acid levels, a serotonin metabolite, has been found in depressed patients (Tandberg E 1997) (Mayeux R 1988). The role of dopamine and norepinephrine in depressed patients with PD is not yet understood. It is probable that depression is mediated by neuronal cell loss in dopaminergic, serotonergic and adrenergic pathways. Becker et al. found significantly reduced raphe echogenicity via transdermal sonography in depressed PD patients compared with nondepressed controls adjusted for age and sex. This suggests that alteration of brainstem raphe-basal limbic systems might play a role in the pathogenesis of depression in PD (Becker T 1997). There is speculation on whether depression might be a part of the PD disease.

Depression in PD contributes to a great impairment of psychosocial, motor and and functional performance. This leads to reduced quality of life, higher level of care dependency and increased caregiver burden. It is shown that 58% of the observed variation of quality of life could be attributed to depression compared with only 17% for the management of physical
symptoms (Global Parkinson's Disease Survey 2002). Several studies have shown that depression in PD patients is more common than in healthy individuals. The main symptoms of depression include loss of interest, a low mood and a feeling of worthlessness or guilt, as well as somatic symptoms such as loss of appetite, sleep disturbances, psychomotor retardation and altered facial expression.

Depression in PD often remains undertreated (Ravina B 2007) (M. P. Weintraub D 2003). One of the factors explaining this might be the difficulty of diagnosing depression in PD patients. The psychomotor slowing and lack of affect often seen in depression might resemble the bradykinesia and masked facial expression seen in PD. Also somatic features of depression such as lack of appetite, sleep disturbance and difficulty with concentration are commonly seen in patients with PD that do not have depression (S. P. Dag Aarsland 2012). As the symptoms of PD and the symptoms of depression overlap, it makes it difficult to clinically tell the two diagnoses apart.

In addition to this, the features of depression in PD patients differ slightly from the clinical depression in patients without PD. In PD it seems that patients suffer from a lack of energy, irritability and psychomotor slowing more than guilty and failing feelings (Ehrt U 2006). Also the sex ratio male:female is 1:1 as compared with 1:2 in the general population (Rickards 2005). Suicide occurs at about the same rate in PD as in the general population (Stenager EN 1994). Also, depression in PD may develop during periods of dopamine deficiency, “off-periods”. This is when the dopaminergic medication wears off and symptoms re-emerge (Storch A 2013).

There is little research on the course of depression in PD. A study by Starkstein et al from 1992, that included 18 PD patients only, found that among patients diagnosed with major depression, over 50% still had major depression after one year of follow-up. 33% still had minor depression and only 11% were in remission. They also found a correlation between major depression symptoms and rapid cognitive decline (S. E. Starkstein 1992) (S. P. Dag Aarsland 2012). Another study from Belgium assessed the level of depression in early PD patients every 3 month over a 12-18 month period. About half the patients who had depression at baseline, experienced remission of their depressive symptoms. High depression score at baseline, older age and longer duration of PD were associated with lower likelihood of remission (Ravina 2009).

3.2 Anxiety in PD

Anxiety is, in addition to depression, one of the most common non motor, psychiatric symptoms in PD. Anxiety contributes to reduction in quality of life, higher levels of care dependency and increased caregiver distress, just as depression (Global Parkinson's Disease Survey 2002) (Hanna 2012). Also, anxiety seems to be under-diagnosed and undertreated probably related to overlapping motor and cognitive symptoms with Parkinson’s disease as well as diagnostic imprecision that makes it difficult to diagnose anxiety in this patient group (Weintraub 2003) (Gallagher 2010).
Clinically, significant anxiety is reported to occur in between 20% to over 50% of the PD patients, and more frequent than expected in the elderly population (S. R. Richard IH 1996) (Shulman LM 2002) (Dissanayaka 2010). Anxiety and depression also have been found to co-occur and it has been reported depressive disorder in 76-92% of the PD patients diagnosed with an anxiety disorder. Anxiety disorder was also present in 67% of PD patients with depression (S. R. Starkstein 1993) (M. R.-H. Menza 1993).

Patients with PD experience generalized anxiety disorder (GAD) as well as panic disorders and social phobias with a prevalence of 30% (Stein 1999) (Nuti 2004) (Vazquez 1993). Anxiety contributes to mental and somatic discomfort, as well as to existing motor symptoms and fluctuations. The presence of anxiety often co-exists with with somatic preoccupation or somatization, although the correlation has not been studied (Siri 2010).

The theories of the mechanism of anxiety in PD is discussed in a review by Chen et Al, 2014. He concludes that overall little is known and that anxiety is attributed to a combination of medical, neurochemical and psychosocial phenomena. Anxiety seems to be more severe in PD than in related groups, and PD patients are at a greater risk of developing anxiety before the PD diagnosis. The same review discusses that episodic anxiety has been associated with motor fluctuations and that, during “off”-phases, patients may experience anxiety that dissipate during the “on”-phases. However, this does not necessarily correlate. Neurochemically, degeneration of subcortical nuclei and ascending dopamine, norepinephrine and serotonin (5-HT) pathways within the basal ganglia-frontal circuits may be responsible for symptoms of anxiety (Chen 2014).

3.3 Depression and anxiety in MSA

There has been described significant depression and anxiety in patients with MSA, but there are limited studies and literature on the topic and the data is based on a few studies only. A study assessing depression in MSA patients was done by Kao et al in 2009. They then used the Geriatric Depression Scale on patients with PD and MSA and found that 50% of the MSA patients had depression and 33.3% had anxiety, compared to 87.5% of PD patients having depression and 62.5% having anxiety (Kao 2009). These results was confirmed in 2010, in a study including 286 patients with MSA. The study looked at the subjective health status in the patient group. The patients completed the EQ-5D and Hospital Depression and Anxiety Scale. 43% of the patients with MSA had probable depression and 37% had probable anxiety. The most important association with subjective health status was with depressive symptoms, which accounted for 29% of the EQ-5D variance in the MSA patients (A. M. Schrag 2010). The high amount of MSA patients suffering from anxiety and depression as well as the association with depression and subjective health suggests that depression has a major impact on the health of the MSA patients and addresses the importance of further research on this topic.
4 Comparison of depression and anxiety in MSA and PD

As described earlier, anxiety and depression are some of the most common non-motor symptoms in both MSA and PD. These two symptoms account for a great reduction in quality of life in both PD patients (Global Parkinson’s Disease Survey 2002) and MSA patients (A. M. Schrag 2010). Traditionally, these two diseases have been understood as mainly motoric diseases, but recent research has shown that non-motoric symptoms might play a greater role in the diseases than previously known.

Studies has shown that the onset of depression in PD can occur at any time, even precede the motor symptoms (Ishihara 2006) of PD in up to 30% of the patients (Santamaria J 1986). The non motoric phenotype of PD patients have recently been put into groups, one of them being the “Park depression/anxiety group”. The group has the subgroups anxious depressed, depressed and anxious. Generally, the anxious subgroups seem to develop earlier and at a younger age than depression, which occurs at an older age with a later onset (Sauerbier 2016). There is not much research on the timeline of depression in MSA, but symptoms might occur a bit later than in patients with PD. However, more research is needed on this topic.

A study by Pilo et al from 1996 compared depression in 12 patients with MSA with 12 patients with PD. Although there was more severe motor disability in patients with MSA compared with patients with PD, they concluded that depression in MSA was not more common than depression in PD. They used the Beck Depression Inventory (BDI) scale and the scores between the two groups did not differ significantly (Pilo 1996). Fetoni et al concluded with the same in 1999 using the Hamilton Depression Rating Scale (HDRS) (Fetoni 1999).

There is little literature on anxiety and depression in MSA, which makes it hard to make any definite conclusion on how these psychiatric symptoms actually impact the patients with MSA and how the course of the symptoms develops over time.

A retrospective study by Balas et al (Balas 2010) analysed the impact of mood, anxiety and depression on cognitive functions of MSA patients compared with PD patients and healthy people. The results are listed in table 2. As the table shows, the MSA-P and PD patients reported significantly increased state anxiety, trait anxiety and depression than controls. MSA-C patients reported significantly higher state anxiety (the level of anxiety experienced during the time of the examination) compared to controls. The study also found a correlation between anxiety and depression and cognitive decline.
Table 2 Independent t tests of mood characteristics of the patients and the controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (N = 10)</th>
<th>MSA-P (N = 15)</th>
<th>MSA-C (N = 10)</th>
<th>PD (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score</td>
<td>Score</td>
<td>Score</td>
<td>Score</td>
</tr>
<tr>
<td>State anxiety</td>
<td>27.2 ± 6.6</td>
<td>38.4 ± 11.7</td>
<td>39.5 ± 10.0</td>
<td>42.6 ± 6.2</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>35.0 ± 4.4</td>
<td>45.4 ± 12.3</td>
<td>41.4 ± 12.7</td>
<td>45.2 ± 5.28</td>
</tr>
<tr>
<td>Depression</td>
<td>5.3 ± 5.2</td>
<td>13.2 ± 7.6</td>
<td>13.1 ± 10.7</td>
<td>10.2 ± 3.9</td>
</tr>
</tbody>
</table>

* P < 0.05
** P < 0.001

Table 2 (Balas 2010)

Literature describes that depression in PD often remains undertreated (Ravina B 2007) (M. P. Weintraub D 2003). Possibly because one of the one cardinal symptoms of PD, bradykinesia, might look the same as symptoms of depression in the PD patients. (S. P. Dag Aarsland 2012). This is not described in the literature of MSA, but it is likely to think that patients suffering from the MSA-P diagnosis might express a similar bradykinesia to the PD patients and therefore also mimic and overlap the symptoms of depression. In this case it is likely to believe that depression also might be underdiagnosed in patients with MSA-P.

An interesting study done by Kao et al in 2009, is comparing the cognitive and neuropsychiatric profiles of individuals with PD, MSA and DLB (Dementia with Lewy Bodies). The three diagnose share α-synuclein immunoreactivity and have overlapping signs and symptoms. Kao et al found that the groups had similar neuropsychiatric profiles of increased depression and anxiety. The results are listed in table III. The same study concluded that because these α-synuclein disorders share similar neuropsychiatric features on most notably depression and anxiety, there might be possible to monitor the symptoms and target the interventions. However, more studies are needed to understand the underlying pathology responsible for anxiety and depression in these groups (Kao 2009).

Table III

Table III from Kao et al 2009 (Kao 2009)
5  Treatment of anxiety and depression in PD and MSA

5.1  Treatment of depression in PD

There has been performed several RCTs addressing how to treat depression and anxiety in PD. The results have been highly variable (Seppi K 2011). This relates to several issues, including a small number of patients recruited, short treatment periods and diversity in methods used. This is discussed in a review by Connolly et al from 2014. As Connolly points out, a wide range of endpoints have been utilized which makes comparisons between studies using the same drugs challenging. Varying inclusion criteria also makes comparison hard. There is no diagnosis-specific drug available for depression or anxiety in PD. Management of these symptoms relies on use of antidepressants developed for general mood disorders (Connolly 2014).

Current pharmacological treatment of depression in PD generally reflects the treatment of depression in the general population, as it is believed that the pathophysiology is similar. However, dopaminergic cell loss in addition to serotonergic and noradrenergic cell loss occurs in PD and this is the fundamental neurodegenerative process in PD (S. P. Dag Aarsland 2012).

As previously described, the symptoms of depression in PD may occur during “off-periods”, (Storch A 2013) and therefore it is important to note when the symptoms occur as this may have an impact on the treatment. If the patient develops depressive symptoms during the “off-period”, first try to adjust the dopaminergic treatment to avoid “off-periods”. This can be done by dividing their total dose into smaller, more frequent doses or through the addition of other medications to increase their total dopamine intake (levodopa, dopamine agonists) or by prolonging the effect of their current medication (Catechol-O-methyltransferanse inhibitors or MAOB-Is) (Connolly 2014).

5.1.1  Antidepressants

Antidepressants traditionally have been the first-line treatment of depression in PD. Currently there are four major groups of antidepressants:
- tricyclic and related antidepressants, TCAs (e.g. amitriptyline, imipramine, nortriptyline)
- selective serotonin reuptake inhibitors, SSRIs (e.g citalopram, sertraline, fluvoxamine)
- serotonin-noradrenaline reuptake inhibitors, SNRIs (e.g venlafaxine)
- monoamine oxidase inhibitors, MAOIs (e.g phenelzine, moclobemide)

The TCAs and MAOIs inhibits the reuptake of noradrenaline and serotonin increasing their functional availability. The SSRIs has greater potency and selectivity for inhibiting the reuptake of serotonin. All antidepressants produce unwanted effects including drowsiness, dry mouth and urinary retention and cardiac-arrhythmias, gastro-intestinal upset as well as the risk of overdose in vulnerable patients (Ghazi-Noori S 2009).
Connolly et al reviewed the treatment of depression in PD in 2014. As Connolly points out, SSRIs are often used to treat PD depression because of, theoretically, fewer side effects than other classes of antidepressants. However, double blind RCTs do not show superior benefits of SSRIs over other medication classes (Connolly 2014). A large double blind RCT comparing venlafaxine (SNRI) and paroxetine (SSRI) suggests that SNRIs are similarly effective to SSRIs with no difference in tolerability (M. M. Richard IH 2012). Moreover, Connolly finds that in RCTs TCAs are shown superior to SSRIs despite of potential anticholinergic side effects. However, Seppi et al concluded, based on all studies up to 2013, that nortriptyline, desipramine and paroxetine are equally efficacious treating depressive symptoms in PD. Venlafaxine was also found efficacious (Seppi 2011).

Unfortunately, there are few high-quality, large RCTs to date that examine the use of antidepressants for depression in PD. Rocha et al systematically reviewed this in 2013 and only managed to find six double blind RCTs that fitted the inclusion criteria. The six trials included six serotonin and norepinephrine reuptake inhibitors, SSRIs (two sertraline, two citalopram, and two paroxetine), two SNRIs (venlafaxine) and two tricyclic antidepressants, TCAs (desipramine and nortriptyline). The trials ranged from 4.5-12 weeks and depression was evaluated by either the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale. After analysing all six studies, Rocha et al could not find any statistically significant superiority of antidepressants over placebo. However, in the sensitivity analysis, when low-quality studies were excluded, antidepressants were superior to placebo. (Rocha 2013).

Sandoval-Rincon et al. reviewed the treatment of major depressive disorder in PD in 2015. They concluded with SSRIs, SNRIs and TCAs being good treatment strategies for depression in PD. Nevertheless, they found that a low number of studies and the lack of a homogenous methodology used to assess outcome, complicated a statistical analysis and getting a conclusion based on a meta-analysis. The review concluded that there was insufficient evidence to recommend specific pharmacological treatment for depression in PD and that more clinical studies are needed (Sandoval-Rincón 2015).

### 5.1.2 Dopamine agonists

The dopamine agonists are a group of synthetic agents directly stimulating the dopamine receptors. These drugs are direct agonists and bypass the nigrostriatal dopaminergic pathway and directly stimulate the post-synaptic receptors in the striatum. Also they do not require conversion and storage by degenerated nigrostriatal neurons, which gives them a theoretical advantage over levodopa. (Leentjens 2011)

Dopamine agonist that are used in treating motor symptoms in PD are all D2 receptor agonists and there is a high concentration of these receptors post-synaptically in the striatum (Uitti RJ 1996). However, in PD, dopaminergic deficiency is also established in the mesolimbic and mesocortical pathways. These structures are involved in reward mechanisms and mood regulation and may play a central role in depression in PD (Willner 1983). Since the frontal cortex and the mesolimbic dopaminergic system contains lots of D3 receptors (a subtype of the D2 receptor), both animal and human studies have suggested a for D3-receptors in the pathogenesis and treatment for depression. (Dikeos DG 1999) (Basso AM 2005).
While antidepressants have for some been a standard treatment for depression in PD, dopamine agonists have recently been suggested as an alternative treatment. (Fernandez HH 2010)

The effect of dopamine agonists on depression in PD have been evaluated in one open-label study (Rektorova I 2003) and two double blind studies (P. W. Barone P 2010) (S. L. Barone P 2006). All three studies looked at pramipexole (non-ergoline dopamine agonists, D2 receptor agonist with a preference for the D3 subtype) compared to placebo, to sertraline and to pergolide as add-on to levodopa therapy. The conclusion in all studies was that pramipexole and sertraline was efficacious, while pergolide was not. However, in 2011, Leentjens reviewed the data for the current dopamine agonists, including pramipexole. He concluded that the evidence for treating depressive symptoms or a major depressive disorder in PD with dopamine agonists is insufficient. It was not possible to establish a clinically significant benefit using dopamine agonists. Also, given the possible side effects of dopamine agonists, such as hallucinations, psychosis, excessive daytime sleepiness and impulse control disorders, it is hard to recommend the use of dopamine agonists over SSRIs, TCAs or cognitive behavioural therapy (Leentjens 2011). Leentjens suggested that therapy with dopamine agonists should only be tried when depression develops with reduction or cessation of dopaminergic therapy or in early PD when the extent to which motor dysfunction is contributing to low mood is uncertain.

5.1.3 Transdermal patch

Rotigotine transdermal system is a non-ergoline dopamine receptor agonist. It is administered transdermally via patch, resulting in stable plasma levels over 24h. A post hoc analysis of RECOVER (Randomized Evaluation of the 24-Hour Coverage; Efficacy of Rotigotine) concluded that this patch may improve the symptoms of depression. (Chaudhuri 2013).

5.1.4 Other pharmacological options

Other pharmacological medications currently suggested for depression in PD:
- Mirtazepin is a new-generation antidepressant. It is a presynaptic alpha-2-adrenocoreceptor antagonist that increases norepinephrine and serotonin levels. There is little research on the effects on depression yet, but there has been described an effect in case reports (Weiser R 2004).

- Bupropion. Dual norepinephrine and dopamine reuptake inhibitory action. So far described in case reports only. This medication does not have the serotonergic side effects seen in SSRIs, SNRIs and TCAs (weight gain, sedation, sexual dysfunction) and may therefore be better suited to treat depression in PD. (Zaluska M 2011) (Raskin S 2010).

5.2 Treatment of anxiety in PD

There is little research on anxiety in PD. Most of the management of anxiety is based on observational studies, expert opinion and clinical guidelines for anxiety disorders in patients without PD. To date there is no specific pharmacological treatment for anxiety disorders in
PD patients (Walsh 2001). Pharmacologically, there are many drugs that possess anxiolytic properties, but benzodiazepines, SSRIs and buspirone are the only ones that have been evaluated for the treatment of anxiety in PD. However, all of the studies firstly assessed depression and had anxiety as secondary outcome. This means that all patients were depressed, but not all of them anxious. (J. J. Marsh 2014) An evidence-based review published by Movement Disorders Society in 2011 found insufficient evidence for the treatment of anxiety in PD to make any recommendations (Seppi K 2011).

5.2.1 “On”- and “Off”-periods

Anxiety may be present continuously in PD patients or in “off-periods”. Anxiety might also be present in the transition from “on” to “off”. As for depression related to wearing off of dopaminergic medication, anxiety occurring of the same reason might also respond to alteration of dosing regimen or addition of an adjunctive PD therapy, such as a Catechol-O-methyltransferase inhibitor or MAOB-I. In addition, rapid-acting subcutaneous apomorphine can be effective for off-period related anxiety. (Factor 2004). However, when anxiety is present in the “off”-state, it is important to treat the motor symptoms before the anxiety (A. Schrag 2004). Thus, it is important to adjust the anti-parkinsonian medication before initiating therapy for the anxiety (F. A. Ferreri 2006).

5.2.2 Benzodiazepines

Benzodiazepines are often used as a therapeutic option for anxiety in the general population. However, there are only one RCT from 1975 addressing this in the PD population. This study found that Bromazepam, a long acting benzodiazepine, improved psychic and somatic (i.e tremor) symptoms of anxiety (Casacchia 1975).

However, special care must be taken in PD patients as Benzodiazepines are thought to act by binding to A gamma-aminobutyric acid (GABAA) receptors and then potentially inhibiting neurotransmission. (Möhler 2002). Benzodiazepines with shorter half-life, such as alprazolam, lorazepam or oxazepam are preferred to avoid drug accumulation and minimize side effects (L. B. Marsh 2003). Common side effects, especially in elderly patients are associated with unfavorable effects on alertness, cognition and gait, and an increased risk of falls (Cumming 2003). Also, clinicians should be careful treating patients with Benzodiazepines due to the risk of abuse and dependence. Therefore the use of benzodiazepines should be limited to as little as possible and to no longer than two weeks (Hanagasi 2005).

5.2.3 Buspirone

Buspirone is a partial agonist of the 5-HT receptors type 1A (5-HT1A). The 5-HT1A receptor inhibits the firing rate of the 5-HT neurons and are located both pre-synaptically (raphe nuclei) and post-synaptically (limbic and cortical regions). (L. B. Marsh 2003). Buspirone has an anxiolytic effect thought to be caused by the decrease of activity in the 5-HT receptors, type 2A and 2C. (Bond 2003). Clinically response in anxiety usually occurs after two weeks of administration. When being administered in low doses (10-40 mg/day), buspirone shows
anxiolytic effects as well as reducing L-DOPA-induced dyskinesia’s without causing sedation or motor-impairment (Bonifati 1994). However, when administered in high doses (i.e. 100 mg/day), buspirone can worsen motor symptoms of PD and cause nausea and insomnia (F. A. Ferreri 2006). Buspirone is therefore a drug that needs to be given in a correct dose, not too much or too little, to have the wanted effect.

5.2.4 SSRIs and SNRIs

SSRIs are well known used in treating depression. However, they can also be used in treating anxiety, although many clinicians only use them when depression coexists or is associated with anxiety. Selective serotonin reuptake inhibitors (SSRIs) and NA and 5-HT reuptake inhibitors (SNRIs) raise the levels of neurotransmitters in the synaptic cleft. This is often disrupted in PD and the drugs improve the neurotransmission (F. A. Ferreri 2006).

As for the other drugs mentioned earlier, there are no studies on using SSRIs for anxiety syndromes in PD. In a recent RCT placebo-controlled study that lasted for 12 weeks, they found no significant differences in treatment effect between placebo, paroxetine and venlafaxine on the secondary outcome of anxiety. However, this study primary addressed depression and the results should therefore be interpreted with care (Richard 2012).

Furthermore, data from uncontrolled studies suggest that SSRIs are effective for anxiety in PD (M. M. Menza 2004) (Tarcey 1998) (Shulman 1996). The weakness in all of these studies is however that anxiety only have been measured as a secondary outcome only. This doesn’t give us high quality data and clinicians can not rely on these studies alone to recommend SSRIs for anxiety patients in the PD-group.

Generally, the SSRIs are are well tolerated. Possible side effects might be producing an initial increase in anxiety, insomnia, nausea, agitation, akathisia, diarrhea/loose stool and somnolence. Occasionally, SSRIs may worsen tremor and chronic use is associated with and increased risk of developing endocrinologic and metabolic adverse effects such as hyponatremia, sexual dysfunction and weight gain (Health 2013).

5.2.5 Tricyclic antidepressants (TCAs)

The TCAs acts to inhibit the reuptake of NA and 5-HT and therefore increasing the levels of the transmitters in the synaptic cleft (Kessel 1995). By increasing both noradrenaline and serotonin, the TCAs compensate for the noradrenergic and serotonergic losses associated with PD, which contribute to anxiety manifestations. Actually, by acting at both noradrenaline and serotonin the TCAs tend to be more efficacious in treating anxiety in PD than the SSRIs (B. D. Weintraub D 2011). However, once again there are no RCTs addressing the effect of TCAs on PD patients with anxiety. Due to the lack of significant evidence, we can not conclude or generally recommend TCAs over any other medication in treating anxiety in PD-patients.

5.2.6 Tetracyclic antidepressants

Mirtazepin was mentioned under the chapter of treating depression in PD. The drug is a new-generation antidepressant. It is a presynaptic alpha-2-adrenooreceptor antagonist that increases norepineprine and serotonin levels. Hence, the drug addresses two major
pathways that are known to cause anxiety in PD. (Chen PH 2008). There has been described an effect on depression in PD-patients treated with Mirtazepin, but there might also be a secondary effect on anxiety in PD-patients. The drug has been shown to treat tremor and dyskinesia caused by L-DOPA therapy and additionally have secondary effects on treating anxiety (Lemke 2008). As Mirtazepin acts on both the NE-system and the 5-HT system by reuptake inhibition, this may possibly cause secondary improvements on motor symptoms that are worsened by anxiety. Improvements in dyskinesia caused by L-DOPA may function by the same mechanism as buspirone – blocking exogenous dopamine production by binding serotonergic terminals. Hence, this would decrease the anxiety symptoms that fluctuate with dyskinesia and L-DOPA motor fluctuations (Coakeley 2014). Reported side effects are sedation, dizziness, sleep disturbance and hallucination (Chen PH 2008).

5.2.7 Electroconvulsive treatment

For patients with severe, medication resistant anxiety or when the anxiety disorder is life-threatening, electroconvulsive therapy should be considered. The therapy is given in series. (Marino 2013)

5.3 Treatment of anxiety and depression in MSA

As for MSA, there is even less research and RCTs existing addressing the treatment of anxiety and/or depression than in the PD-group. Most of the existing therapeutics currently used are based on expert experience and do not meet scientific evidence standards (Flabeau 2010).

A review from 2010 lists current first line treatment of depression in MSA as psychotherapy, SSRIs and levodopa. Alternative treatments listed are electroconvulsive therapy and repetitive transcranial magnetic stimulation (Flabeau 2010).

Selective serotonergic reuptake inhibitors (SSRIs) are the most prescribed antidepressant treatment. In a double-blind placebo-controlled, paroxetine was found to improve motor abilities in the upper limbs and speech. However, the degree of depression was not significantly influenced by paroxetine. This was explained by the lack of severe depression in patients included in the study and a short observation period (Friess E 2006).

Levodopa may slightly increase mood disorders in MSA according to Fetoni et al 1999. However, this trial included 12 MSA patients and only one had major depression. Overall they found the mood of the MSA patients to increase slightly, but the results are based on a very small group and should therefore be interpreted with care (Fetoni 1999).

Electroconvulsive therapy may be considered in MSA patients with major depression who don’t respond to any antidepressants. This is described in case reports only (Shioda 2006) (Nicholas Chia 2014)

Also, psychological support is necessary, as well as nursing care and family education (Hardy 2008)
5.4 Cognitive behavioural therapy

Cognitive behavioral therapy (CBT) is a nonpharmaceutical approach for treating psychiatric symptoms in patients. It is based on the construct that individuals with anxiety and depression hold distorted cognitions. The aim of CBT is to provide a structured approach to help individuals identify maladaptive thoughts contributing to emotional discomfort and to replace them with alternative thoughts (Dobkin 2011). There exist few studies on CBT treatment in PD-patients and none in MSA-patients. However, one should believe that both groups would have an effect of CBT treatment, but due to the lack of evidence, this is only speculations.

5.4.1 CBT for treating anxiety and depression in PD

Once again, there is little research on the effects of CBT on treating depression and anxiety in PD-patients. There has been described that CBT have most effect when not only addressing the depressive and anxiety symptoms, but also addressing the motor symptoms (Aarsland D 2009). A blinded RCT performed by Dobkin et al in 2011 studied the effect of the CBT treatment on PD-patients. A group of PD patients without dementia was places either into a CBT group or a placebo group. They used a program adapted for PD patients where they also provided caregiver education to reduce anxiety and depression at home. The clinical monitoring consisted of two follow-up calls and an evaluation using the Hamilton Anxiety and Depression Rating Scale. They found significant improvement in the CBT group in depression, anxiety, motor decline, and quality of life. These results even suggest that addressing the anxiety and depression in PD-patients also might improve the motor symptoms and the quality of life (Dobkin 2011). However, more research is needed to conclude and recommend this treatment in general to PD-patients.
6 Discussion and conclusion

The main goals with this study have been to compare anxiety and depression in Parkinson’s disease and Multiple system atrophy to find out what treatment is normally given to the two patient groups with these symptoms and whether the treatments given are based on statistically significant and reliable studies.

By doing a non-systematic search in PUBMED, relevant reviews were included. By reading the reviews, primary sources and trials were found.

Literature suggests that in treatment of depression, the SSRIs seems to be most commonly used in both groups. There is, however, not evidence suggesting that SSRIs are more effective than other medications. For the PD group, some studies actually suggested that TCAs are more effective than the SSRIs in treating depression. However, other studies found no difference between antidepressants and placebo in PD-patients. Dopamine agonists have been suggested as an option, as have the transdermal dopamine agonist patch Rotigotine, but there is no significant evidence on this to date. Mirtazepin (an antidepressant) and Bupropion (norepinephrine and dopamine reuptake inhibitor) may also have effect, but there is also a lack of evidence backing this information.

As for anxiety in PD, benzodiazepines are often used and are found to have some effect. However, due to side effects and possible dependence this medication should be used with care. Busprione (a partial 5-HT agonist) may have effect, the same goes for SSRIs and SNRIs and for TCAs, but there are no RCTSs addressing the use of any of these drugs on anxiety in PD-patients and therefore there is a lack of significant evidence to back this information. The drug Mirtazepin is also mentioned as a treatment for anxiety, but there is no significant evidence backing this information either. Last, electroconvulsive treatment may also work in drug-resistant anxiety.

In the MSA group, very little literature exists on anxiety and depression, but psychotherapy, SSRIs and levodopa are mentioned as possible treatments for both symptoms. Alternative treatments listed are electroconvulsive therapy and repetitive transcranial magnetic stimulation. Cognitive behavioural therapy is found to be efficient in both anxiety and depression in the PD group. There is no literature on this in the MSA group.

There are several issues that makes it hard to make a definite conclusion in this study. Firstly, there is a major gap in literature and trials existing in the MSA group compared to the PD group. Secondly, there is very little literature addressing the treatment of anxiety and depression in the respective groups, once again more in PD than in MSA and more on depression than anxiety. This gives us too little significant evidence to actually make a proper comparison between the groups and the symptoms and thereafter make a conclusion on treatment strategy.

The literature that exist on these topics reflect that non-motor symptoms in Parkinson’s disease and in Multiple System Atrophy have not been given much attention. The lack of large double blind RCTs addressing the symptoms and treatment of anxiety and depression in the two groups is conspicuous, being absolutely absent in the MSA group. Only a very few trials have been done in the PD group.
As for the trials and studies done, an issue is the lack of consistency in defining depression and anxiety. Different authors use different diagnostic scales and some even invented their own scales for the specific study. This makes it hard to compare the studies and hard to make evidence based clinical guidelines on treatment of anxiety and depression in MSA- and PD-patients.

Another issue is that a lot of the studies include a low number of patients. This might be due to the amount of people having the disease in the case of MSA. However, it is hard to conclude on the efficiency of a treatment based on small studies only.

**Conclusion:** As a consequence of low number of studies and a lack of large RCTs addressing the treatment options of anxiety and depression in MSA and PD, practical management is currently based on empirical evidence only. There is insufficient evidence to recommend any treatment for depression and anxiety in the PD and MSA groups. More clinical studies are needed.
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