Physical Comorbidities and Mood Disorders in Older Adults

14

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Abstract

Physical health and mood disorders are intertwined in many ways, and several somatic diseases are directly related to mood disorders. Physical disease may present with depressive symptoms, and several physical symptoms are part of depression. Physical problems may lead to or cause depressive disorder and vice versa. Medication prescribed to treat mood symptoms may have side effects resulting in somatic comorbidity, and somatic medication may provoke mood-related side effects.

In older adults with mood disorders, physical comorbidity is the norm rather than the exception, and over time the mood disorder might act in concert with physical comorbidities to accelerate aging and cognitive deterioration.

Side effects are among the most important reasons for patients to stop taking their medication. Polypharmacy, age, and somatic comorbidities are key factors known to increase side effects. Medical conditions coexisting with a mood disorder may be truly comorbid, related to the treatment of the mood disorder, or a combination of both. For directions on treatment of these somatic comorbidities, the differentiation is important.

Physicians treating older adults with mood disorders should be aware that the physical health of these patients is an important aspect of their lives as it may influence their need for care and quality of life and complicate treatment and the course of the psychiatric disease. Comorbid conditions should be carefully assessed, and treatment options should be chosen taking into account these comorbid states, minimizing side effects and treatment burden.

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Contents

General Physical Health and Comorbidity in Late-Life Depression

In epidemiological studies, an increased physical morbidity and mortality are shown in depressed older people, not only in severely depressed patients fulfilling the criteria of major depressive disorder (MDD) (Association 2013) but also in those with a so-called mild or minor depression, also referred to as "clinically relevant depressive syndrome" (Lyness et al. 2006; Penninx et al. 1999; Beekman et al. 1997). A variety of factors and mechanisms play a role in these associations.

Here, we will discuss a variety of these factors, the consequences for physical and mental well-being, and the recommendations for the clinician. We use the term "depression," including MDD as well as clinically significant depressive syndrome.

Depression itself is characterized by a broad spectrum of symptoms in the physical, psychological, and social functioning domains. This may cause difficulty in diagnosing the depression as well as comorbid physical disorders that may coexist independently but often are associated with the depression. Particularly in older depressed people, somatic problems tend to get more attention than psychiatric problems, as well from the doctor as the patient himself, which may lead to underestimating the severity and hampering the treatment of the depression (Mitchell et al. 2010). But also vice versa, the existence of depression may lead to underdiagnosis and undertreatment of somatic conditions, due to diminished seeking for medical help and motivational problems in medical treatment in depressed patients (Braam et al. 2005).

As stated in the introduction, somatic comorbidity is the rule in older adults with mood disorders, and therefore it is important to apply a broad perspective in diagnostic evaluation directed toward both psychological problems and physical complaints and diseases.

Physical Diseases with Symptoms of Depression

Symptoms of depression and medical conditions may overlap. Fatigue and loss of energy, often prominent features in depression, are seen in many physical disorders in late life, e.g., chronic infections, cardiovascular and neurological diseases, and cancer. Decreased appetite and weight loss may occur in gastrointestinal problems, chronic infections, or cancer. Sleep disturbances may be due to pain or Parkinson's disease. The latter can be confusing in many ways with a lot of overlapping symptoms, such as motor slowing, starting problems, diminished facial expression, and emotional lability. Concentration and memory problems can be rather severe in depression but may also be a sign of a developing dementia. Psychomotor slowing, weight gain, and increased need of sleep are also found in hypothyroidism, whereas agitation, nervousness, weight loss, and sleep problems may be symptoms of hyperthyroidism. Thyroid dysfunction is rather common in women over 50 and often starts with psychological changes as mentioned above or may be very similar to the normal aging process instead of the well-known symptoms of hair loss, myxoedema, and changes of voice and pitch (Bensenor et al. 2012). There is discussion about the clinical significance of subclinical hypothyroidism (described as no clinical symptoms but abnormal laboratory findings) as a cause of depression and the necessity of treatment; this will be addressed for in more detail later on in this paragraph. Also other hormonal disturbances such as Cushing's syndrome, Addison disease, hyperparathyroidism, pheochromocytoma, or tumors with endocrine activity may mimic depression by altering mood, sleep, appetite, psychomotor function, and energy level.

Physical Problems Due to Depression

Depression may lead to physical problems. Depressed patients often have a less-healthy lifestyle, with decreased food intake, less balanced diet, higher use of tobacco and alcohol, and diminished physical exercise (DiMatteo et al. 2000; Kroenke 2003). This may lead to nutritional deficiencies, weight loss or weight gain, and diminished physical condition, which in turn may lead to new physical problems such as balance problems, falls and fractures, and decreased ability to recover from trivial health problems such as influenza. Due to delay in the search for medical help in case of physical problems in depressed patients, treatment of preexisting or newly emerging physical diseases is hampered (DiMatteo et al. 2000). This may lead to undertreatment of all kinds of common medical conditions such as hypertension, diabetes, pain, and cardiovascular and pulmonary problems (Wahlbeck et al. 2011). Thus, depressed patients tend to spiral down in this reinforcing loop of "depression lifestyle" and physical deterioration, leading to the abovementioned elevated morbidity and mortality.

But unhealthy lifestyle and diminished motivation for seeking medical treatment are not the only mechanisms leading to physical problems. In the Longitudinal Aging Study Amsterdam (LASA), a large population-based study in older Dutch people, a higher cardiac mortality rate was found in the depressed subsample, even in the absence of preexisting cardiovascular disease, and independent of the abovementioned lifestyle differences (Penninx et al. 1999). The finding that depression is an independent risk factor for cardiovascular morbidity and mortality was found in other studies as well (Anda et al. 1993; Regulies 2002; Wassertheil-Smollers et al. 2004; Kamphuis et al. 2006; van der Kooy et al. 2007; Kendler et al. 2008; van Marwijk et al. 2015). In congestive heart failure, depression showed a 2.5-fold risk for severe cardiac complications and death (Lett et al. 2007). In a review on heart failure followed by depression, MDD was a predictor for subsequent all-cause mortality (Fan et al. 2014). In the oldest old (age over 85), depression was found to be related to all-cause mortality as well as cardiovascular mortality (Vinkers et al. 2004). In the Epidemiologic Catchment Area (ECA) study, a large epidemiologic study in the United States, depression at baseline was found to be a risk factor for myocardial infarct (OR 4.5), CVA (OR 2.7), DM type II (OR 2.2), and arthritis (OR 1.3) in the 13-year follow-up (Eaton et al. 2006).

In depressed patients, several changes in the cardiovascular system are found that may contribute to the increased cardiovascular morbidity and mortality. An important finding is a diminished heart rate variability in depression, which may be a sign of diminished flexibility and responsiveness of the cardiac function and thereby lead to coronary heart disease (Rottenberg 2007).

Another finding is an elevated level of platelet adhesion and aggregation in depressed patients, which may increase the risk for cardiovascular events (Laghrissi-Thode et al. 1997). Interesting and promising is that SSRIs have an effect on platelet function and seem to protect against the development of atherosclerotic plaques and arterial thrombosis (Pollock et al. 2000).

Changes in the diurnal cortisol variation and in the responsiveness and feedback system in the HPA axis found in depression may lead to hypertension, which is in turn a risk factor for cardiovascular damage throughout the body.

Physical Problems Leading to Depression

In general, people with physical illness are found to be more vulnerable to depression, which in turn leads to prolonged stay in the hospital, worse functional recovery of the illness, and a higher morbidity and mortality (Creed and Dickens 2007; Mavrides and Nemeroff 2013). High prevalence for depression in adults of all ages is found for cardiovascular disease (17–47%), CVA (14–27%), Alzheimer's disease(11–50%), Parkinson's disease (29–52%), diabetes (9–26%), cancer (22–38%), chronic pain (21–32%), epilepsy (6–80%), migraine, multiple sclerosis, and HIV/AIDS (5–30%) (Evans et al. 2005; Miller et al. 2008; Patten et al. 2003; Torelli et al. 2006; Rouchell 1996; Mavrides and Nemeroff 2013). In heart disease, high percentages of depression were found for coronary problems (20%), congestive heart failure (30–40%), and after bypass operation (50%) (Whooley 2006). Risk for depression after a myocardial infarct is related to the degree of dysfunction of the left ventricle (Melle et al. 2005). Depression after CVA is associated with the intracerebral localization of the ischemic lesion with a greater risk in right-sided lesions (Shimoda and Robinson 1999; Robinson and Starkstein 1990).

Except for HIV/AIDS, all physical diseases mentioned above are rather common in older age. Together with other conditions often found in older persons, such as chronic infections, malnutrition, anemia, rheumatoid arthritis, and chronic pulmonary disease, these physical conditions are considered to be important predictors of depression in late life (Cole and Dendukuri 2003; Djernes 2006). It is not clear how often the presence of (new) physical illness is the main cause of depression, and in most cases the increased prevalence of depression is considered to be the result of more common, not disease-specific, factors. Particularly the functional consequences of physical disease, such as pain, mobility problems, worsening of daily functioning, feelings of loss of control, and changes in roles, are considered to be important in the association with depression (Beekman et al. 1997; Rodin et al. 2005).

In neurological diseases, and in particular in Parkinson's disease and dementia, a high prevalence of depression is found, and psychological as well as more neurobiological factors are supposed to play a role. Scientific background of this phenomenon will be addressed for later on in this chapter.

General Physical Health and Comorbidity in Late-Life Bipolar Disorder

Bipolar disorder has been conceptualized as multisystem disease, rather than brain specific as comorbid medical illnesses in bipolar disorder might be viewed not only as the consequence of health behaviors and of psychotropic medications but rather as

an early manifestation of a multisystemic disorder (Leboyer and Kupfer 2010; Leboyer et al. 2012). Physical comorbidity complicates outcome in late-life bipolar disorder (Lala and Sajatovic 2012). Only a few studies have studied physical comorbidities in bipolar older patients (Lala and Sajatovic 2012); therefore, knowledge on physical comorbidities in bipolar disorder is mainly derived from studies in younger or mixed-aged samples. There are no longitudinal studies, and only five studies of somatic comorbidity have included 50 or more bipolar older patients. A review of comorbidity in late-life bipolar disorder found an average of 3–4 medical comorbidities (Lala and Sajatovic 2012), including metabolic syndrome (up to 50%), hypertension (45–69%), diabetes mellitus (18–31%), cardiovascular disease (9–49%), respiratory illness (4–15%), arthritis (16–21%), endocrine abnormalities (17–22%) (Lala and Sajatovic 2012), as well as atopic diseases such as allergic rhinitis and asthma (6–20%), which can greatly impact quality of life (Tsai et al. 2009; Lala and Sajatovic 2012). With each decade of life, the number of physical comorbidities is reported to increase to 11 comorbid somatic conditions in those older than 70 years (Fenn et al. 2005).

Older bipolar patients have a greater burden of physical comorbidity than age-matched unipolar depressed peers (Gildengers et al. 2008); however, the overall prevalence of physical illnesses in older patients with bipolar disorder is reported to be comparable to rates in community-based geriatric samples (Lala and Sajatovic 2012). Nevertheless, older bipolar patients have much higher mortality rates, and due to cardiovascular and other physical illnesses, they die on average 10 years earlier than the general population (Westman et al. 2013). Therefore, patients with bipolar disorder who survive into old age likely represent a healthy "survivor" subpopulation. This was also illustrated by a report on metabolic syndrome in older bipolar and schizophrenia patients with rates comparable with healthy elderly (Konz et al. 2014).

Physical comorbidity will limit treatment options for bipolar disorder by drug interactions and altered drug metabolisms. Polypharmacy is also frequent, with 31.7% of patients reported to be on six or more medications (Dols et al. 2014b). As some psychiatric patients have a limited access to physical health care, screening, and prevention (De Hert et al. 2009), their physical health should have the attention of mental health professionals. The recommendations for physical work-up have been summarized by the International Society for Bipolar Disorders (Ng et al. 2009). For older patients with bipolar disorder, screening for side effects and/or complications of medication and evaluating their general physical health is recommended more frequently (two to four times a year) (Ng et al. 2009). In patients using antipsychotics, screening for metabolic syndrome is advised (fasting lipid profile, fasting blood glucose, blood pressure, and waist circumference). Prescriptions of other doctors should be double checked at the pharmacist, and inquiries about over-the-counter medication use are no luxury. Clinicians providing care for bipolar elderly patients should carefully assess for comorbid conditions, choose treatment options that take into account these comorbid states, and minimize side effects and treatment burden. Close collaboration between mental health, primary care, and medical speciality clinicians is strongly recommended.

Physical Comorbidity as a Side Effect of Medication

In this paragraph, an overview is given of the most frequent and most important side effects of antidepressants and mood stabilizers commonly used in late-life depression and bipolar disorder. For more detailed information, particularly on pharmacodynamics and pharmacokinetics, we refer to guidelines and textbooks on psychopharmacology.

Cardiovascular Side Effects

Orthostatic and general hypotension, hypertension, heart conducting problems, and heart frequency changes are often found in antidepressant use. For an extensive overview, we refer to the chapter on "▶ Pharmacotherapy for Mood and Anxiety Disorders" for depression and anxiety disorders in the elderly.

Sedation

Sedation and drowsiness are often seen in antidepressants with strong anti-histaminergic or anti-norepinephrinic effect but may be due to alpha-1-receptor blocking and 5-HT2 receptor antagonism as well. Also anticholinergic or hypotensive effects may play a role, particularly in older patients. Strong sedative effects are found for mirtazapine, trazodone, mianserin, doxepin, and amitriptyline and also to a lesser extent in SSRIs in higher doses. The sedative effect may be enhanced by interaction with alcohol or other sedating drugs. Temporarily lowering of the dose may diminish sedation because tolerance for this effect is developed in the first weeks of treatment. Other solutions are administration of the antidepressant in the evening instead of during the day, or changing to a less sedating antidepressant.

Cognitive Impairment

Cognitive impairment can be distressing for patients and may hamper their compliance to treatment. Several studies have demonstrated that patients with bipolar disorder have impaired functioning across a range of cognitive domains, even after resolution of mood symptoms and independent of pharmacological treatment (Young et al. 2006; Martinez-Aran et al. 2005).

Pharmacotherapy, especially lithium, has been associated with poorer cognitive performance. In a recent review, almost 600 studies were identified concerning the effect of lithium on cognitive performance (Wingo et al. 2009), concluding that lithium appears to have only few and minor negative effects on cognition.

The cognitive effects of valproate and carbamazepine have been scarcely evaluated in bipolar patients. Valproate and carbamazepine seem to have roughly the same effect on cognition as lithium (Senturk et al. 2007; Joffe et al. 1988). Lamotrigine

might have a better impact on memory than other anticonvulsants (Daban et al. 2006).

The management of cognitive complaints in bipolar patients is challenging; treatable causes such as clinical or subclinical hypothyroidism should be addressed first. The slowing of cognitive performance ("cognitive dulling") can respond well to dose reduction and/or enhancing thyroid function (Goodwin et al. 2007). Patients may benefit from cognitive remediation therapies combined with lifestyle changes.

In depression, cognitive impairment is found as well. In many patients (reversible), attention and concentration problems are found, sometimes leading to memory problems or mental slowing. Antidepressants may enhance these problems, particularly in the case of anticholinergic or anti-histaminergic side effects.

Neurological Side Effects

(a) SSRIs may cause *extrapyramidal side effects*. Bradykinesia, rigidity, and tremor, and sometimes also acute dystonia and akathisia, have been described for fluoxetine, fluvoxamine, and sertraline. The incidence is low in monotherapy; in most cases SSRIs were combined with antipsychotics, lithium, or TCAs (Jacobson et al. 2007; Carvalho et al. 2016). The advice is to change the antidepressant.

(b) *Tremor* is found in SSRIs, TCAs, trazodone, lithium, valproate, and lamotrigine. The incidence differs in the several studies on antidepressants from almost placebo – level to an elevated risk of 10–20%. Serotonergic stimulation is thought to be the cause. In most cases, habituation is found after 2–3 weeks, and the tremor disappears when the antidepressant is discontinued. Tremor has been reported in up to 65% of patients using lithium (Gelenberg and Jefferson 1995) and in 1–6% of patients using VPA. Management of a medication-induced tremor starts with objective observation of the tremor and an open dialogue to challenge any catastrophic beliefs about perceived impairments (Hallam 2010). Extended-release preparations can reduce tremor. Reducing the use of caffeine and nicotine can have a positive effect. Beta-adrenergic blockers (e.g., propranolol) and vitamin B6 are effective in reducing tremor (Miodownik et al. 2002).

(c) *Myoclonus* is frequently found in TCAs and SSRIs and may lead to speaking problems (myoclonus of the jaw) or sleep problems (myoclonus of arms or legs during the night). Dose reduction sometimes leads to diminishing of these symptoms.

(d) Most antidepressants lower the threshold for *seizures*. For grand mal seizures, an incidence of 0.1–0.6% has been found, and the risk is higher for patients with a history or family history of epilepsy. Particularly TCAs and maprotiline are found to elevate the risk of seizures, with risks up to 15% in higher doses (maprotiline >300/day).

Gastrointestinal Side Effects

(a) With a prevalence up to 80% is a *dry mouth*, one of the most frequent side effects of TCAs and lithium, and it may lead to caries and infections of the mouth and to poorer adherence to treatment (Jacobson et al. 2007; Kennedy et al. 2001). The anticholinergic properties (of the TCAs) are thought to be the cause, although a dry mouth is also reported in SSRIs and trazodone use (Carvalho et al. 2016). This symptom should decrease after a couple of weeks using the antidepressant, but it often persists and may be the reason for patients to stop their medication.
(b) *Constipation* is often caused by the depression itself but may be aggravated by antidepressants with anticholinergic properties.
(c) *Nausea and vomiting* together with *intestinal cramps and diarrhea* are a result of anti-5-HT2 effects and are typically found in serotonergic antidepressants (SSRIs, trazodone, and moclobemide), lithium, and valproate with an incidence ranging from 10% to 60%. Diminished appetite is found in fluoxetine and fluvoxamine; it is dose related and presents particularly in the first weeks of treatment. These complaints are not found in TCAs. Coated or slow-release tablets appear to be better tolerated. To prevent initial nausea, it is best to slowly increase the dose. A temporary reduction is the best management option if nausea occurs, followed by a more gradual increase. Persistent nausea can be treated with the histamine-2 (H2) antagonist famotidine or cimetidine (Stoll AL 1991).

Urinary and Genital Tract

TCAs often cause problems in emptying the bladder, due to a heightened sphincter tonus, an anticholinergic effect. This may lead to urinary retention, in particular in older men with prostate hypertrophy and of course when a combination of anticholinergic drugs is used. It is not dose related and often a change of antidepressant is necessary.

Sexual side effects of medication can be either primary (specific sexual effects) or secondary (e.g., caused by weight gain, hypothyroidism) (Demyttenaere et al. 1998). Sexual dysfunction is found in 30% of patients that use TCAs, consisting of decrease of libido, prolonged time to orgasm, and erectile problems. SSRIs have a high prevalence (50%) of sexual dysfunction with the same problems as the TCAs, and also ejaculatory problems. Mirtazapine and moclobemide show less sexual adverse effects.

Lithium appears to have minor effects on sexual function (Ghadirian et al. 1992). The literature on sexual side effects of anticonvulsants is almost entirely restricted to their use in epilepsy and thus confounded by the fact that epilepsy itself is associated with sexual dysfunction (Harden 2008; Smaldone et al. 2004). Specific recommendations to manage medication-induced sexual dysfunctions are lacking. A correlation between sexual side effects and serum level of lithium could not be

demonstrated (Ghadirian et al. 1992), but thriving for the lowest effective level is always advisable (Sienaert and De Fruyt 2001). A number of pharmacological agents (cyproheptadine, yohimbine, amantadine, bethanechol, neostigmine, PDE5 blockers [sildenafil, tadalafil, vardenafil]) have been proposed in the treatment of specific dysfunctions, but apart from the PDE5-blockers, the clinical experience with these drugs in these indications is limited. Physicians and patients should be encouraged to discuss sexual side effects, in order to increase compliance and quality of life.

Weight Gain and Metabolic Syndrome

Weight gain is a frequent and significant problem in psychiatric patients even without prescription of agents associated with metabolic syndrome. TCAs, mianserin, and mirtazapine often (up to 50%) lead to weight gain, due to the antihistaminergic properties of these antidepressants (Kennedy et al. 2001). It may be a reason for discontinuation of the treatment. Some patients experience an increased appetite, but the weight gain is also contributed to a slowing of the basal metabolism. Nonselective or irreversible MAO inhibitors show weight gain as well, due to the same mechanism.

Weight loss and loss of appetite are found in fluoxetine and fluvoxamine and are probably due to an increased basal metabolism (Carvalho et al. 2016).

Clinically significant weight gain (i.e., >7%) is more frequent in patients on olanzapine than on lithium (McKnight et al. 2012). However, a 5–10% weight gain is reported by 25–50% of patients using lithium (Keck and McElroy 2003; Goodwin et al. 2007). Two to 3 lbs weight gain can be expected as a result of temporary fluid retention. Weight gain may be caused by increased appetite, lithium-related subclinical hypothyroidism, lower metabolic rate, increased food intake secondary to improved mood, and polydipsia resulting in drinking large amounts of high-caloric drinks (Torrent et al. 2008). As for all lithium-induced side effects, weight gain is dose dependent and less likely at plasma levels below 0.8 mmol/l (Sachs and Guille 1999). After 7-year of follow-up, it was reported that weight occurred during the first 1–2 years of prophylactic lithium treatment and then remained constant (Vestergaard et al. 1988). A 1-year follow-up study found that 155 obese patients with bipolar I disorder lost weight (−4.2 kg) while taking lamotrigine and gained weight (6.1 kg) while taking lithium (Bowden et al. 2006), while there was no significant weight change in 399 non-obese patients. The prevalence of weight gain with valproate treatment is estimated to occur in 3–20% of patients and ranges between 3 and 10 kg over a period of 3–12 months (Pijl and Meinders 1996; Bowden 2003). Studies on weight gain in carbamazepine-treated patients show controversial results, and with the paucity of long-term follow-up data in bipolar patients, weight gain due to carbamazepine seems unlikely (Torrent et al. 2008).

Therapeutic options to reduce weight include dietary counseling, and exercise programs should be available for all bipolar patients (Nemeroff 2003), even prior to starting mood stabilizer therapy. Antipsychotic use in older patients is associated

with higher rates of hyperglycemia (Lipscombe et al. 2009) as well as increased mortality and risk for cerebrovascular accidents (Setoguchi et al. 2008; Wang et al. 2005).

In a recent meta-analysis, the rate for metabolic syndrome in patients with schizophrenia, bipolar disorder, and major depressive disorder of all ages was reported to be 32.6% (Vancampfort et al. 2015). Compared with matched general population controls, there was an increased risk for metabolic syndrome in psychiatric patients. The relative risk was not different between the diagnostic groups. Older age, higher body mass index, and the use of antipsychotics, especially clozapine and olanzapine, were associated with an increased risk for metabolic syndrome.

Studies of metabolic syndrome in older patients, as a complication of using atypical antipsychotics, are very limited. In 100 older patients with schizophrenia and bipolar disorder, the prevalence of metabolic syndrome was not higher than in healthy controls and not related to the use of a specific class of antipsychotics (Konz et al. 2014). Possibly, older patients with bipolar disorder who survive into old age represent a healthy "survivor" subpopulation.

Thyroid and Parathyroid

A Cochrane review on lithium for maintenance treatment of mood disorders concluded that there were insufficient data on specific side effects to allow meta-analysis, except for hypothyroidism which occurred in 5% of patients on lithium and in none of those on placebo (Burgess et al. 2001). In a recent meta-analysis, lithium was associated with increased risk of endocrine side effects such as hypothyroidism and hyperparathyroidism (McKnight et al. 2012). Lithium inhibits thyroid hormone secretion by several different mechanisms. CBZ and VPA were shown to have this same effect, however less frequent and particularly when combined with lithium (Gau et al. 2010). In the majority of patients, compensatory mechanisms operate and prevent the development of hypothyroidism. Risk factors for development of hypothyroidism include iodine deficiency, cigarette smoking, and presence of thyroid antibodies. The prevalence of thyroid autoantibodies among lithium-treated patients varies across studies and may be more associated with affective disorder than with lithium (Kupka et al. 2002). Women, especially beyond the age of 50, more often express thyroid autoimmunity (Bocchetta et al. 2007), which makes them especially at risk for lithium-induced hypothyroidism (Kirov et al. 2005; Bocchetta and Loviselli 2006). Most patients are diagnosed with hypothyroidism in the first years of lithium treatment (van Melick et al. 2010; Johnston and Eagles 1999). The wide range of prevalence rates of hypothyroidism in lithium-treated patients (0–23%) is explained by differences in criteria (overt vs. subclinical hypothyroidism) and study population (gender, iodine intake, proportion of subjects with autoimmunity) (Bocchetta and Loviselli 2006). Up to 2% of lithium-treated patients require treatment with levothyroxine (Kirov et al. 2005; Bocchetta and Loviselli 2006).

A retrospective analysis of laboratory data with a median follow-up of 3 years (max. 28 years) on patients using lithium was found an increased risk for hypothyroidism, with women, especially younger women, and patients with diabetes at higher risk (Shine et al. 2015). Lithium levels over 0.6 mmol/L were associated with increased risk for adverse effects.

Monitoring of clinical symptoms provides useful guidance for treatment in addition to values of TSH or free T4, since management of even subclinical hypothyroidism may improve outcomes among bipolar patients (Kleiner et al. 1999; Najafi et al. 2015).

A meta-analysis of 14 observational studies found a 10% increase of calcium and parathyroid hormone concentrations in lithium users (McKnight et al. 2012). The risk for elevated adjusted calcium concentration was not raised with lithium treatment (Shine et al. 2015), only total calcium concentrations were. Women aged 60 and over were most at risk. It is recommended to measure calcium (total and adjusted) concentrations in all patients on lithium therapy at baseline and at least annually thereafter.

Kidney

The effect of lithium on renal function has been the subject of several large population-based studies and meta-analyses in the past decade (McKnight et al. 2012; Kessing et al. 2015; Shine et al. 2015). Rates of kidney failures appear lower than previously reported and feared, possibly as a result of modern treatment principles (Aiff et al. 2014). Here, we will describe the two most common forms of kidney disease associated with lithium use: nephrogenic diabetes insipidus and chronic renal failure.

Nephrogenic diabetes insipidus is the result of lithium inhibiting the stimulating effect of antidiuretic hormone on the resorption of water in the collecting ducts of the nephron (Bendz and Aurell 1999). This causes polyuria, dehydration, thirst, and compensatory polydipsia. On average, urine-concentrating ability is reduced by 15% of normal maximum after long-term lithium use (McKnight et al. 2012) with a urinary production of more than 3 L a day. Other causes of polyuria and polydipsia such as diabetes mellitus have to be excluded as well as central diabetes insipidus and primary stimulation of the thirst center following lithium use (Cox and Singer 1975). Primary (psychogenic) polydipsia occurs predominantly in schizophrenia (Mercier-Guidez and Loas 1998), and dry mouth as a result of the anti-cholinergic side effects of drugs such as tricyclic antidepressants has to be considered.

Renal function is measured by glomerular filtration rate (GFR). Stage 3 chronic renal failure is defined as a GFR <60 mL/min per 1.73 m^2; at this point patients may develop symptoms, such as high blood pressure, anemia, and/or early bone disease. Only a very small subset of patients with stage 3 chronic renal failure will progress to end-stage renal failure; the risk has been estimated to be 0.5–1.0% (Tredget et al. 2010; Bendz et al. 2010).

In long-term lithium users, the mean GFR reduction is −6.22 mL/min over a mean observation time of 1 year (McKnight et al. 2012). Lithium users have a greater risk for renal failure compared to general population (Shine et al. 2015; Kessing et al. 2015). In bipolar patients the risk for renal failure is increased when using lithium or anticonvulsants and not with antipsychotics or antidepressants (Kessing et al. 2015). No effect of stable lithium maintenance therapy with a mean duration of 55 months was found on the rate of change in GFR over time; nephrotoxicity was determined by episodes of acute intoxications, duration of therapy, and cumulative dose (Clos et al. 2015).

In elderly patients renal failure is more prevalent, which can be attributed to the use of supratherapeutic lithium levels, accidental intoxications, co-medication (mostly diuretics and ACE inhibitors), medical comorbidity (mostly diabetes mellitus and hypertension), and age-related renal function decline (Rej et al. 2012). The casual relationship of long-term lithium use with renal dysfunction (Bendz et al. 2010; Paul et al. 2010) remains to be confirmed in geriatric populations (Rej et al. 2013). In older patients using lithium, potential correlates of renal disease include the use of diuretics and ACE inhibitors and higher lithium levels in the context of inadequate lithium monitoring (Ghose 1991). The most robust renal risk factors in older adults are diabetes, hypertension (Coresh et al. 2007), and age-related renal decline (Rej et al. 2012).

Thus, especially in the relatively large group of lithium users with only mild loss of renal function, treatable risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and proteinuria have to be addressed (Boton et al. 1987; Aiff et al. 2014). Throughout lithium prophylaxis, it is essential to monitor renal function in lithium levels at regular intervals, keeping lithium levels as low as possible, and avoid intoxication.

A serum creatinine of ~200 μmol/l (Manjunath et al. 2003) or GFR <40 mmol/l (Lepkifker et al. 2004) is considered to indicate a point of no return, and when approaching this point, one should consider stopping lithium prophylaxis (Presne et al. 2003; Markowitz et al. 2000). When this is not an option, impeding entry of lithium into the principal cells of the collecting ducts by blocking epithelial sodium channel with amiloride or drugs with a similar mode of action would provide a logical strategy to decelerate further renal lithium toxicity, with simultaneous reduction of the lithium dose. However, this strategy has not yet been proven effective; amiloride 5–20 mg/day has levels I and II evidence in the acute treatment of nephrogenic diabetes insipidus (Batlle et al. 1985; Bedford et al. 2008). Induction of increased potassium levels can be managed with potassium binders, e.g., Sorbisterit.

Syndrome of Inappropriate ADH Secretion (SIADH)

Particularly SSRIs but also TCAs may cause hyponatremia and disturbed secretion of antidiuretic hormone (ADH). Symptoms that may point to this disturbance are fatigue, sleep problems, and lethargy, but these are also symptoms of depression and thus are sometimes missed as a new somatic problem. Older persons appear to be

more vulnerable for this syndrome, and the use of other drugs that affect the same system, such as diuretics, increases the risk. It is not dose related, and crossover effects are found, which means that change to another SSRI will probably lead to the same problem. In older people, it is advised to check serum sodium before starting an SSRI, and again some weeks after the optimal dosage is found, and to be alert on symptoms of hyponatremia during the first 4 weeks after the start of the SSRI.

Eyes

Visual problems are due to decreased ability of the circular muscle of the lens to accommodate, an anticholinergic effect. This may cause blurred vision and impairment in reading and may worsen when the antidepressant is combined with other anticholinergic agents. There is an (rarely seen) elevated risk of (worsening of) glaucoma, and consultation of an ophthalmologist is advised (Carvalho et al. 2016).

Liver

Elevated levels of alkaline phosphatase, transaminases, and bilirubin are sometimes seen in treatment with antidepressants (Voican et al. 2016). It is not clear if this is a real pathophysiological change and what it means. Most of the changes have a temporary character. Rarely intrahepatic cholestasis is found, a severe condition with a peak incidence in the second month of treatment. Symptoms include sudden fever or abdominal pain, and discontinuation of the antidepressant is necessary. This complication is found in many antidepressants, and recent warnings have been given for agomelatine and mirtazapine (Stadlmann et al. 2012; Gahr et al. 2014).

Asymptomatic elevation of transaminases during treatment with valproate is seen in about 40% of cases. Abnormal liver function tests are mostly nonprogressive and not necessarily an indication for ceasing valproate. Transaminases will often normalize after simple dose reduction (Ghozzi et al. 2011). Hepatological complications leading to valproate discontinuation are estimated to occur in about 1:15,000 cases (Lackmann 2004). Severe hepatotoxicity is rare (0.01%) and is potentiated by the combination with other antiepileptic drugs (Ghozzi et al. 2011).

Hyperammonemia in the absence of abnormal liver function has been reported in 16–100% of patients treated with valproate (Chicharro et al. 2007), even with therapeutic serum levels, but is asymptomatic in most cases (Chicharro et al. 2007; Dealberto 2007; Hung et al. 2011; Shan et al. 2009). In rare cases it can lead to changes in consciousness and encephalopathy: valproate-induced hyperammonemic encephalopathy (VIHE). First symptoms occur most frequently within weeks after initiating or increasing the dose of valproate, but cases occurring during several years of maintenance therapy are also reported. Most frequent signs and symptoms include (flapping) tremor, ataxia, drowsiness, lethargy, disorientation, and "inappropriate behavior" (Dealberto 2007; Shan et al. 2009). The nonspecific presentation is frequently overlooked and regarded as a worsening of the psychiatric condition or as

side effect of concomitant medication (Shan et al. 2009). EEG shows symmetrical generalized slowing (Dealberto 2007). VIHE seems to occur equally in both genders. Possible risk factors include polypharmacy, mental retardation, vegetarian diet, urea cycle enzyme deficiency, and carnitine deficiency. The mechanism of VIHE remains unknown. The mean increase of serum ammonia level is about double the baseline level (Chicharro et al. 2007). Although no clear correlation was found between valproate serum levels, ammonia levels, and clinical symptoms, decreasing dose or discontinuing is advised.

Blood

Heightened levels of eosinophilic cells or lowered levels of leucocytes are often observed in all antidepressants, in about 10% of patients taking carbamazepine (Bertolino 1990; Sobotka et al. 1990) and rarely in patients treated with valproate (Lackmann 2004). It is mostly a harmless and temporarily effect.

There is no evidence that transient leukopenia progresses to aplastic anemia. The elderly (Askmark and Wiholm 1990) and patients whose total neutrophil or leucocyte count is low before treatment initiation (Bertolino 1990; Sobotka et al. 1990) are at increased risk of developing blood dyscrasias. Seldom seen but life threatening is agranulocytosis, which may develop after several weeks of treatment, with symptoms of sore throat, fever, difficulty in swallowing, infections in the mouth, or enlarged lymph nodes. Immediate discontinuation of the antidepressant is necessary, and antibiotics are given for prophylaxis.

Skin

Most patients experience dermatological side effects as distressing, and without proper attention and treatment, there is an increased risk for poor compliance. A frequent complaint in TCAs is perspiration, often during the night or in waves, and is due to blockage of alpha-1-receptors and/or serotonin reuptake inhibition (Kennedy et al. 2001; Bet et al. 2013). It is reported to lead to feeling uncomfortable, particularly in social contact with other people, and to disturbance of the sleep.

Exanthema is seen in 2–4% of patients with a TCA or fluoxetine and 6–8% in maprotiline. It is harmless, and changing the antidepressant may improve the complaints (Kennedy et al. 2001).

Although a meta-analysis showed no significant difference in the prevalence of skin disorders between patients given lithium and those given placebo (McKnight et al. 2012), in controlled trials, 3.4–45% of patients treated with lithium developed dermatological side effects, mainly acne and psoriasis (Yeung and Chan 2004). Acne is one of the most common side effects; it can develop within weeks after the initiation of lithium treatment. Psoriasis may develop after a refractory period of few weeks to several months. The incidence has been reported to be 1.8–6%. Preexisting psoriasis should not be regarded as a contraindication to lithium

prescription, but patients with a positive family history of psoriasis should be monitored carefully (Pande et al. 1986).

A benign rash occurs in 8.3% of lamotrigine patients in controlled settings ($n = 1{,}198$) and 13.1% of patients ($n = 257$) in an open-label setting (Calabrese et al. 2002). A serious rash as part of Stevens-Johnson syndrome or toxic necrolysis was reported 0.0% and 0.1%, respectively.

Intoxications and Anticholinergic and Serotonergic Syndrome

Intoxications in older people may be due to prescription of too high dosages (for this particular patient) and can be evaluated by monitoring serum levels. Of course, suicidal gestures with medication may also lead to dangerous serum levels.

Intoxications with TCAs can be dangerous because of the anticholinergic properties, and a broad range of symptoms can be found, like suppression of breathing and aspiration pneumonia, conduction disturbances leading to arrhythmias, heart block, PVCs, tachycardia, disturbances of consciousness, seizures, and coma. Treatment is possible, but often hospital admission and intensive care treatment are necessary.

Intoxications with modern antidepressants like SSRIs are less dangerous but may lead to the serotonergic syndrome.

Intoxication with lithium is, as in younger adults, based on clinical judgment and not lithium serum levels alone. Supratherapeutic lithium serum levels and intoxicates are major risk factors for renal failure and should be avoided at all times.

Anticholinergic Syndrome

In toxic doses of antidepressant medication with strong anti-muscarinic potential, a confusional state (delirium) may develop, consisting of anxiety, agitation, disorientation, hallucinations, myoclonus, seizures, hyperthermia, stupor, and even coma. Typical for the anticholinergic syndrome, and discriminating from other causes of delirium, are specific systemic symptoms such as tachycardia, widened pupils, a warm and dry skin, and dry saliva. Often prodromal confusion and agitation are seen, particularly during the night, and nightmares. The risk for the development of an anticholinergic syndrome is elevated when the antidepressants are combined with other psychotropic drugs with anticholinergic potential, such as an anti-Parkinson medication and some antipsychotics. Treatment consists of lowering the dose or discontinuation of the antidepressant, and in severe cases physostigmine 2–4 mgs i.v. or i.m. can be given.

Serotonergic Syndrome

This serious condition is due to stimulation of serotonin neurotransmission, and in most cases a combination of two or more serotonergic agents is necessary to provoke this syndrome. Symptoms are hyperthermia, motor symptoms (particularly extrapyramidal:

rigidity, cogwheel phenomenon, tremor, myoclonus, hyperreflexia, ataxia, agitation), autonomous disturbances (tachycardia, tachypnoea, tension changes, perspiring, nausea, diarrhea, urine incontinence), and consciousness changes (sedation, somnolence, anxiety, agitation, disorientation, hallucinations, seizures). The serotonergic syndrome may be life threatening or even lethal. It may be difficult to diagnose, because it looks like other deliriums or malign neuroleptic syndrome. Treatment consists of discontinuation of the medication.

Discontinuation of Antidepressants, Withdrawal Symptoms, and Interactions with Other Drugs

Please refer to the chapter on "► Pharmacotherapy for Mood and Anxiety Disorders" for depression and anxiety disorders in the elderly.

Subtypes of Mood Disorders Directly Related to Physical Health

Parkinson's Disease and Depression

Depression is a common comorbidity in Parkinson's disease (PD). In the literature prevalence up to 50% is found; however, most studies report prevalence between 20% and 30% (Evans et al. 2005). Depression may be found at any stage of the Parkinson's disease. In a longitudinal study with 400 Parkinson patients, 20% had a depression and approximately half of cases showed a persistent course. Risk factors were female gender, more severe disability, more severe motor fluctuations, autonomic and cognitive dysfunction, poorer nighttime sleep, and daytime sleepiness. Apart from motor fluctuations, depressive symptoms in PD were mainly associated with non-dopaminergic factors (Zhu et al. 2016). This underscores the idea that Parkinson's disease is not only a dopamine problem but that other neurotransmitter systems are involved as well, evoking all kinds of symptoms among which disturbances of mood and affect. The process starts in the medulla oblongata and from there spreads out to the higher regions (Braak and Tredici 2009). Although dopamine dysregulation often provokes the first obvious signs, i.e., motor signs such as rigidity and/or tremor, serotonergic dysregulation may occur earlier and cause depression and lability. In a longitudinal study in general practice, 9% of patients had depression in 3 years before the diagnosis of Parkinson's disease was confirmed, against 4% in the non-Parkinson patients (Leentjens et al. 2003).

Psychological factors may play a role as well, through the whole process. In the beginning or even before Parkinson's disease is diagnosed, the (future) patient may notice subtle changes in functioning that make him insecure or anxious. In later stages of the disease, when functioning is more hampered or motor problems are more difficult to treat, it may also increase the risk for depression.

The symptom profile of depression in Parkinson's disease may vary. A kind of "mental slowing" may occur, with apathy, lack of initiative, bradyphrenia, difficulty getting started in the morning, concentration problems, and diminished interest. However, also severe melancholic depression with vital symptoms and psychotic features may be seen, as well as in the beginning or even prodromal phase of the Parkinson's disease as later on in the disease process.

As mentioned above, many Parkinson symptoms are similar to depressive symptoms, and it is very important to investigate mood and affect in the case of Parkinson's disease because of the high common prevalence. Depression should be regarded as a separate problem and treated along the guidelines for depression. Antidepressant medication may worsen the Parkinson symptoms, and close collaboration with the neurologist is necessary. Electroconvulsive therapy (ECT) is often very effective and may improve the Parkinson symptoms as well as the mood symptoms.

Dementia and Depression

In 25–35% of patients with dementia, depressive symptoms are found, and in 10–20% criteria for MDD are fulfilled (Enach et al. 2011). Depression can be found in every stage of dementia, although in end stages, it is rare or very difficult to diagnose. Cognitive problems, such as concentration problems, memory problems, and problems in executive functioning, are often found in late-life depression. Sometimes these problems persist when the depression goes into remission, and this is found to be a predictor for the development of dementia (Kessing and Nilson 2003; Korczyn and Halperin 2009). Particularly in the early phase of dementia, it can be difficult to differentiate between depression and dementia. More elaborate diagnostic procedures, with interviewing the patient and the family on symptoms and course of the depression, gathering information on the psychiatric history, and neuropsychological tests may be helpful. However, many symptoms of depression are also found in several types of dementia, and sometimes it is not possible to differentiate between these two disorders. In that case it is important to treat a possible depression and follow the course of symptoms and functioning over time.

Depression in dementia may have a psychological basis, e.g., a psychological reaction to the perceived changes in cognitive function or to expected problems in the future. However, neurobiological processes play a role as well. In the case of white matter changes, as seen in vascular dementia but also in Alzheimer's dementia, a cluster of symptoms is found consisting of diminished interest, lack of initiative, lessened emotional reactivity, psychomotor slowing, and decreased ability to enjoy (Alexopoulos et al. 2008). Although motivational problems are most prominent and mood symptoms may be less clear, the criteria for depression are often met. Specific criteria for depression in Alzheimer's disease were proposed and have more emphasis on social withdrawal (Olin et al. 2002). More information on this so-called vascular depression can be found in the next paragraph.

Neurotransmitter loss, a core problem in many types of dementia, may also lead to depressive symptoms, particularly when there are disturbances in the

monoaminergic systems (serotonin, dopamine, (nor-)epinephrine, and melatonin) (Reinikainen et al. 1990). These neurotransmitter systems are all involved in several aspects of mood disorders.

Medial temporal lobe atrophy (MTA) or hippocampal atrophy and global cortical atrophy (GCA) are characteristic features in Alzheimer's dementia but are also seen in depression (Sheline et al. 2003). This finding may point to a common mechanism for depression and dementia, with differential clinical manifestations in the cognitive and mood domains.

Stress and the elevated levels of cortisol in depression may contribute to the higher risk of dementia in depressed persons, with the notion that this may cause death of hippocampal cells (Sapolsky et al. 2000).

Vascular Depression

In the late 1990s of the past century, the "vascular depression" hypothesis was postulated by Alexopoulos and Krishnan (Alexopoulos et al. 1997; Krishnan et al. 1997). This vascular depression was considered to be a subtype of late-life depression, found in patients with late-onset depression and substantial deep white matter hyperintensities on brain MRI. A typical clinical presentation was found, with psychomotor retardation, apathy, and more neuropsychological impairment, particularly executive dysfunction, compared to early-onset depression and a poorer response to treatment. The cerebrovascular disease was supposed to be the cause of this type of depression, with structural damage to the frontostriatal circuits that are involved in emotion regulation and executive functioning. It is not clear if the poor treatment response is associated with the white matter abnormalities, or with the executive dysfunction (Taylor et al. 2006; Sneed and Culang-Reinlieb 2011). As already mentioned, response to pharmacological treatment is worse than in other types of depression. In a study on post-stroke depression, nortriptyline was found more effective than fluoxetine, but the anticholinergic properties of the TCAs may be a problem in these patients with higher cerebral vulnerability (Robinson et al. 2000). SSRIs were found to even deteriorate the depression, showing a worsening compared to placebo (Sneed et al. 2010). Electroconvulsive therapy however has shown to be effective in this type of depression.

Next to treatment of the depression, management of the cardiovascular risk factors is important. Hypertension, diabetes mellitus, hyperlipidemia, smoking, and alcohol use should be evaluated and treated when necessary. A problem may be that antihypertensive medication may have a depression-inducing effect (see the chapter below section on "Medication-Induced Depression").

Metabolic Depression

A subtype of depression, defined by a specific pattern of symptoms among which weight gain instead of weight loss and increased need of sleep instead of diminished

sleep, appears to be connected with specific disturbances in metabolic processes and inflammation: the so-called metabolic depression.

In the Netherlands Study of Depression and Anxiety (NESDA), adult patients with an atypical depression had significantly higher levels of inflammatory markers, body mass index, waist circumference and triglycerides, and lower high-density lipid cholesterol than persons with melancholic depression and controls (Lamers et al. 2013).

In a Dutch community-based study, a high plasma level of the inflammation factor interleukin-6 (IL-6) was associated with an increased prevalence of major depression in late life, independent of age, chronic diseases, cognitive functioning, and antidepressants (Bremmer et al. 2008).

In the Netherlands Study of Depression in Older persons (NESDO), inflammatory factors (C-reactive protein, IL-6) and metabolic factors (waist circumference, triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure, fasting glucose) were investigated in depressed patients aged 60–93. Patients with atypical depression presented with metabolic upregulation, whereas immunometabolic downregulation was found in depressed patients with less severe symptoms and those with late-life onset (Vogelzangs et al. 2014a). In patients in NESDO using antidepressants, inflammatory and metabolic dysregulations predicted a more chronic course, suggesting a negative effect on antidepressant treatment response (Vogelzangs et al. 2014b). In the longitudinal Health, Aging, and Body Composition (HABC) Study, obesity, in particular visceral fat, increased the risk of onset of significant depressive symptoms in older men, suggesting that specific mechanisms might relate visceral fat to the onset of depression (Vogelzangs et al. 2010).

So, the presence of increased weight and other metabolic disturbances in depression is probably not a coincidence but part of the pathophysiology of depression, and (visceral) fat may be an active component in the (dys)regulation of affective processes. Screening for and treatment of metabolic factors are advised, also because there may be a link with worse outcome of antidepressant therapy.

Medication-Induced Depression

In the literature, a lot of reports can be found on medication associated with the onset or worsening of depression. Anticonvulsants, medication for Parkinson's disease, migraine and multiple sclerosis, a wide range of cardiovascular medications, anti-infective agents, oncologic agents, corticosteroids, and other hormonal agents are mentioned to play a role in evoking depression or even MDD.

However, for most drugs, only small studies or case reports have been performed, while prospective studies are lacking or did not find an association (Celano et al. 2011).

Furthermore, many of these drugs are given because of diseases that are associated with depression itself, and the link of medication and depression may be a more coincidental finding, not a real causal relationship.

However, there is evidence that some of the agents mentioned above are associated with depression. Furthermore, individual factors such as genetic vulnerability or concurrent medication may cause a depressive syndrome in single patients but not in the general population. It is advised to be alert on temporal associations of depression with the start or change of medication use, to perform an "on-off-on" trial and in case of doubt to change the medication (Dhondt et al. 1999; Celano et al. 2011).

Secondary Mania

Late-life manic symptoms and physical health are highly linked, and different hypotheses have been proposed. Somatic factors may be a true cause of mania (secondary mania), or merely triggering mania as a first manifestation of bipolar disorder in a person with a latent vulnerability, and with or without a previous history of depressive episodes. Somatic comorbidity may also be a coincidental finding without any causal relationship to mania.

Manic symptoms, as disturbed sleep, irritability, and impaired attention, in later life have a broad differential diagnosis including a psychiatric diagnosis such as (late-onset) bipolar disorder and schizoaffective disorder (primary mania) or an organic syndrome such as delirium, dementia, and secondary mania. Late-life mania is not rare; the overall prevalence is estimated to be 6.0% in older psychiatric inpatients with about one third experiencing their first manic episode (i.e., late-onset mania) (Dols et al. 2014a). Although the management of both primary and secondary mania may be similar, the etiology of mania is of importance as the appropriate treatment of secondary mania includes addressing the cause (Krauthammer and Klerman 1978).

The concept of secondary mania was introduced by Krauthammer and Klerman in 1978 (Krauthammer and Klerman 1978) as a condition with manic symptomatology resulting from an underlying medical illness that could develop in people with no history of mood disorder. For manic symptoms to be classified as secondary mania, the patient should have no history of primary mood disorder or evidence of delirium. The list of various neurological conditions, systemic disturbances, and medications that have been described to cause secondary mania is very extensive (Van Gerpen et al. 1999). While it can occur at any age, it is more common in older patients; this is understandable given the higher prevalence of potentially causative medical conditions and treatments in older adults. On the contrary, one could argue that coincidental somatic findings should not be attributed to have caused manic symptoms, since the vast majority of patients with these somatic comorbidities do not develop manic symptoms. Presently data are lacking to label "due to a somatic condition or medication" as specifier in bipolar disorder. As we know from other psychiatric disorders (e.g., schizophrenia), certain substances (e.g., cannabis) can prime the development of a psychiatric disease.

Analogous to delirium, many somatic conditions can cause mania in patients of any age; however, some patients seem more at risk, for example, older patients and patients with vascular non-symptomatic) brain damage; perhaps vascular risk factors

prime these patients to develop manic symptoms without matching bipolar patients in other aspects.

Vascular Mania

Although far less common than depression, mania can occur in 1% of stroke patients, in 2–12% of patients with movement disorders as Huntington's disease, and in patients with epilepsy or infections of the brain (Mendez 2000). Tumors, neurosurgery, and traumatic head injury can result in manic symptoms (Brooks and Hoblyn 2005), occasionally with a delay of up to 12 months before the manic symptoms develop (Jorge et al. 1993; Robinson et al. 1988). Focal brain lesions in the right hemisphere have been associated with mania (Braun et al. 1999).

Steffens and Krishnan (1998) proposed criteria for vascular mania and depression subtype specifiers, and their concept of vascular mania appears to have some overlap with the neurological disinhibition syndrome. Vascular mania is defined as a subtype when mania occurs in the context of cerebrovascular disease or neuropsychological impairment. Late-life mania may occur not infrequently in patients with non-symptomatic) vascular brain damage. Some (Martino et al. 2013; Samame et al. 2013; Schouws et al. 2009) but not all (Subramaniam et al. 2007) reports suggest that late-onset bipolar disorder is associated with significant cognitive impairment. One study noted that those with late-onset bipolar disorder had a greater prevalence of white matter hyperintensities (WMH) in the deep parietal region and basal ganglia compared to bipolar patients with an earlier onset and healthy controls (Tamashiro et al. 2008). In a recent sample of older bipolar patients, including both early and late onset, the self-reported prevalence of cerebrovascular disease was 3%, (Dols et al. 2014a); however, silent cerebral infarctions may be present in over half of older bipolar patients, regardless of age at onset (Huang et al. 2012).

Differentiating between "frontal disinhibition" and "bipolar mania" can be challenging; many symptoms are overlapping; nevertheless, "bipolar mania" may be more characterized by elevated mood and lack of need for sleep, contrary to disturbed sleep. The presence of a positive family history of affective disorder may indicate that a somatic cause resulted in mania by triggering an existing bipolar predisposition (Krauthammer and Klerman 1978).

Conclusion

In older adults with a mood disorder, an inclusive approach with investigation of symptoms of both depression and comorbid physical problems is warranted. It may be hard to disentangle physical complaints from primary mood symptoms, but it is advisable to treat the most important cause of the physical problems, together with treatment of the depressive component, dependent on the severity of symptoms. An example may be a severe depression with psychotic features and hypothyroidism:

restore the hormonal balance and consider an in-patient trajectory, addition of psychological treatment and support, and biological treatment of depression in case of persistence of the depression part.

Other important physical interventions that should be given together with depression treatment may be supplying nutritional deficiencies and treatment of infections. These factors may undermine the physical strength necessary for recovery from the depression. Even surgery for hip fracture may be very important to improve the possibilities for recovery from the depression (as well as for successful revalidation). In daily practice, this may feel as a moral dilemma to give such an extensive treatment to a sad and down old patient, and it is important not to join the defeatist and hopeless attitude often found in depressed patients (and their family).

And of course, it is wise to check the medication for side effects of depression.

Optimizing physical health will include interventions on lifestyle and unhealthy behavior, such as smoking, alcohol, sedentary lifestyle, and overweight. They may be part of the problem in disturbing mood balance and worsen treatment outcome.

Physical disease is a risk factor for the development of depression, and it can be difficult to discriminate a developing depression from the somatic problems that already exist. Indications for depression in somatic disease may be slow recovery or even a fallback, poor initiative, diminished appetite, sleep problems, dependency for functions of daily living, behavioral changes (irritability, drawback), memory problems, mistrust, or delusions.

Physical investigation with special attention to vascular risk factors is advised for every depressed older patient and laboratory tests comprising at least hematological tests, Na, K, Ca, glucose, liver function tests, renal function tests, TSH, vitamin B12 and folate, and other tests when indicated (Baldwin et al. 2002).

It is important to evaluate somatic complaints before the start with antidepressants or other agents, to prevent labeling them wrongly as side effects.

Somatic health is so key in the diagnosis and treatment of mood disorders in older adults that psychiatrists and other mental health workers caring for these vulnerable patients should be educated in somatic medicine as well as in mental health.

Cross-References

▶ Pharmacotherapy for Mood and Anxiety Disorders

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