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Review

Depression in the Context of Medical Disorders: New Pharmacological Pathways Revisited

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Key Words
Depression • Cancer • Inflammation • Diabetes • Dementia • Cardiovascular Disease

Abstract
The depressive state has been characterised as one of elevated inflammation, changed cardiovascular parameters and a deranged metabolic situation all of which holds promise for a better understanding and handling of treatment-resistance in affective disorders as well as for future developments in treatment algorithms. In this context several biomarkers are differentially regulated by antidepressant treatment and connected to metabolic, inflammatory, cardiovascular and apoptotic components of the pathophysiology, i.e. adiponectin, apolipoprotein-B, B-type natriuretic peptide, cortisol, CRP, cysteine, homocysteine, fibrinogen, adiponectin, BMI, glycated hemoglobin A1c, leptin, interferon-gamma, high-density lipoprotein, interleukin interleukin-1alpha, -1beta, -2, -4, -5, -6, -8, -10, -12, -13, -17, insulin-like growth factor-1, low-density lipoprotein, myeloperoxidase, osteoprotegerin, tumour necrosis factor alpha, troponins, triglycerides etc. In this context antidepressants exert different modulatory effects on the outcome, incidence and mortality concerning several severe disorders, i.e. cancer, diabetes, stroke, inflammation, stroke and cardiovascular risk. Vice versa different drugs used in the treatment of these disorders have a favourable effect in depressive states, e.g. statins, aspirine, NSAIDs, pioglitazone, celecoxib, peroxisome proliferator-activated receptor-gamma agonists and minocycline. In this review, actions of different antidepressant treatment strategies on cancer, stroke, diabetes and cardiovascular disorders are shown and the influence on the outcome of the disorders is differentially discussed. In conclusion a hypothetic model for the implication of actual findings in everyday clinical practice is proposed. In this context personalized treatment could be used to tailor treatment to specific individuals according to their clinical endophenotypes. Moreover a potential target for the development of novel intervention strategies might be used.

Introduction

The results from studies from controlled trials concerning elderly patients with medical comorbidities (cardiovascular disorders, diabetes, dementia, cancer) are insufficient [1].

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Depression increases the risk of severe physical disorders such as cancer, diabetes, stroke, inflammation and acute coronary syndrome through multiple molecular mechanisms [2] (see Fig. 1). Moreover, depression has an adverse impact on the course of these disorders with more funcional impairments, more complications, higher mortality and poorer quality of life and compliance. However, depression is often connected with stress and a live style, which implies smoking, low physical exercise, sleep disturbances, less social activities and unhealthy nutrition. These habits again can lead to a significant proportion of inflammatory, atherogenic and metabolic risk factors that might lead to the significant increase of the prevalence and severity of cardiovascular, cancer and metabolic diseases (see Fig. 1). To appropriately manage depression in these patients and increase life quality, outcome of the physical disorder, life expectancy and adherence antidepressant treatment should be provided and has proven to be successful. However, the differential influence of antidepressant strategies on the specific physical disorder is not easy to examine as different antidepressant strategies result (at least in retrospective population surveys) from different clinical subtypes of patients and therefore the influence of depression per se and the antidepressant on the physical disorder is complex and often not separable. Moreover, patients suffering from a medical disorder and are additionally depressed might not be comparable wth patients suffering from a medical disorder who are not depressed as depression per se might separate patients who are stronger affected also from the somatic disorder.

Several biomarkers relevant for different facets of depressive disorders are differentially regulated by antidepressant treatment and connected again to metabolic, inflammatory, cardiovascular and apoptotic components of the pathophysiology, i.e. adiponectin, apolipoprotein-B, B-type natriuretic peptide, cortisol, C-reactive protein, cysteine, homocysteine, fibrinogen, growth-differentiation factor-15, glycated hemoglobin A1c, leptin, high-density lipoprotein, interleukin-6, insulin-like growth factor-1, low-density lipoprotein, myeloperoxidase, osteoprotegerin, tumor necrosis factor-α, troponins, triglycerides [3] (see Fig. 1).

The objective of the present review is to present different hypothesized influences of antidepressants on clinical correlates of different physical disorders and hypothesized pathophysiological mechanisms of medical treatments on depression. In particular the influence of antidepressants on cancer, stroke, diabetes and acute coronary syndrome are shown and the treatment of these physical disorders on the course of depression. This review will ideally enhance our current treatment strategies of associated serious medical conditions and possibly will allow clinicians to develop more advanced and personalized treatment options for these patients in routine practice or at least explain special clinical cases occurring typically in the everyday clinical routine.

In patients with cancer think about tricyclic antidepressants

Depression is common after a cancer diagnosis and is associated with an increased mortality, however, depression is often occurring before the cancer diagnosis and increases cancer mortality [4] (see Fig. 1). Two decades ago, it was hypothesized that antidepressants could alter the course of neoplastic diseases. However, contradictory findings indicated that antidepressants could either have carcinogenic properties or improve the disease outcome. An important aspect of future experiments will be to continue to investigate the signaling networks perturbed by these drugs in cancer cells. For example, in our own experiments, we found that the PI3K mTor pathway might be linked to depressive behavior in mice 5, 6] and man [7, 8]. Therefore antidepressants might evolve their actions far beyond the monoamine hypothesis influencing at ways which are involved in cancer development and progression. Intriguingly, controversial results were reported on the action of antidepressant drugs on immune function. Further hypotheses proposed that antidepressants could

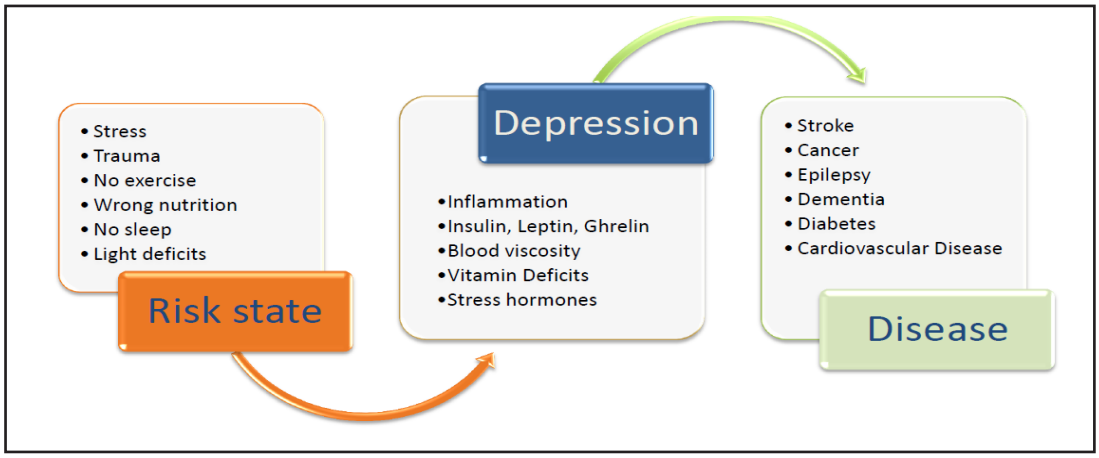

Fig. 1. Depression often occurs with comorbid medical conditions. Common risk factors might leading to both; depression and medical disorders.

indirectly affect cancer prognosis through the modulation of antitumor activity. Here we review the literature in order to elucidate the influence of antidepressants on cancer and immunity. The immune system, i.e. innate immune activation, inflammation and suppression of the immune system have been shown to play a role in the pathogenesis of depression and neoplastic growth. Cancer patients experience a threefold higher rate of depression within the first five years of diagnosis and vice versa depression is associated with increased cancer risk and shortened survival. In this contex cancer patients often need antidepressant treatment and research is needed to determine whether differential antidepressant treatment improves cancer survival. It is essentiell to develop antidepressant strategies that target neurobiological pathways mediating both, oncogenesis and depression and the underlying molecular and cellular mechanisms that influence pathophysiological cascades of both disorders. Several studies suggested that antidepressant use might increase or decrease the risk of cancer occurrence, depending on specific cancer types. Whereas bipolar disorder was not associated in a nationwide Swedish study with increased cancer incidence and with lithium treatment, there was an increased risk of respiratory, gastrointestinal, and endocrine cancer in patients with bipolar disorder without lithium treatment [9].

Colon cancer is one of the most common tumors worldwide, with increasing incidence in developing countries. Patients treated with fluoxetine have a reduced incidence of colon cancer, although there still remains great controversy about the nature of this effect [10]. Experimental evidence indicates that serotonin is associated with both proliferative and pro-carcinogenic effects on colorectal tumors. However, in colorectal cancer, selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and serotonin antagonist and reuptake inhibitors were not associated with increased incidence of the disease in humans [11]. Monoamine oxidase inhibitors were associated with an increased incidence of colorectal cancer and higher cumulative dose of mirtazapine was associated with a decreased incidence of colorectal cancer [11]. Lithium accumulates in the colon and inhibits the enzyme GSK-3beta that possesses anti-carcinogenic effects, however, lithium use was not associated with an overall increased risk of colorectal adenocarcinoma [12].

The “repositioning” of an existing drug to treat a disorder other than the one for which it was originally approved is an example of how extremely large genetic and biological databases are changing the face of medicine [13]. In this context, three novel and still unknown compounds against colorectal cancer were computationally predicted amongst one is citalopram [13]. Citalopram as a potential therapeutic option for patients with colorectal cancer has been verified by *in vitro* assays of clonogenic survival, proliferation, and migration and in a subcutaneous mouse model [14].

Cancer stem cells are the cell population responsible for lung cancer chemoresistance and are a very good model for testing new targeted therapies. Clomipramine is able to potentiate the pro-apoptotic effects of DNA damaging induced agents in several cancer cell lines. Desmethylclomipramine inhibits lung cancer stem cell growth, decreases their stemness potential and increases the cytotoxic effect of conventional chemotherapeutic drugs [15]. Mirtazapine caused a substantial up-regulation of the Lin-7C/β-catenin pathway in metastatic human small cell cancer cell lines and human melanoma-derived cell lines *in vitro*, and up-regulation did not contribute to cellular proliferation. Moreover, the antimetastatic effect of mirtazapine in these metastatic cell lines *in vivo* also was evident in multiple organs of immunodeficient mice with no marked side effects [16].

Furthermore, the antidepressant imipramine has been discussed recently to be potentially effective in combating small cell lung cancer, according to a study in labaratory mice from researchers at the Stanford University School of Medicine [17]. Indeed, basic research studies in mice are suggesting that cisplatin-resistant tumors are still sensitive to imipramine treatment [16]. An increased survival in patients with small cell lung carcinoma possibly linked to imipramine treatment might suggest this drug also in off label use in patients suffering from other tumors, including glioma, colorectal cancer and retinoblastoma, which has been suggested at least by epidemiological studies [18, 19 (see Fig. 2).

Long-term use of tricyclic antidepressants has been associated in a nation-wide study with a reduced risk of glioma but not for serotonin reuptake inhibitors [20]. Hypericin targets multiple mechanisms in human glioblastoma tumor cell lines via unique manners [21]. It induces neuroglial tumor cell differentiation modulating the cytoarchitecture, neuroglial differentiation antigen expression and causes exit from cell proliferation cycles and has been discussed to constitute a novel anti-glioblastoma therapeutic paradigm [21]. Evidence shows that antidepressants decrease cancer incidence of glioblastoma and improve patients'

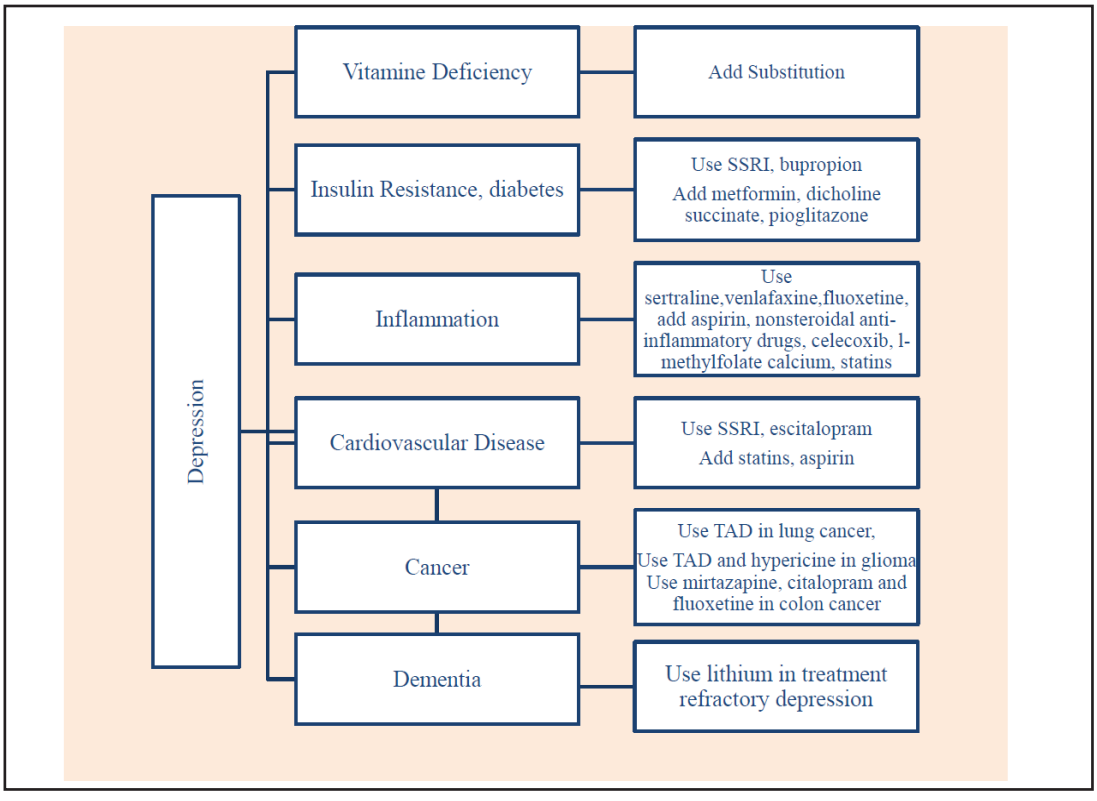

Fig. 2. Depressed individuals with different comorbid disorders should be treated differently.

quality of life [22]. Selectively fluoxetine suppressed the growth of glioblastomas in brains of mice, an effect similar to that produced by temozolomide in preclinical studies, which has been hypothesized to provide a new approach for managing this disease [22].

Paroxetine was associated with a 620 percent increase in the rate of breast cancer in women who had taken it over a four-year period and as the highest inhibitory constant for the P-450-2D6 isoenzyme of all antidepressants which implies an increased probability of oncogenesis [23]. However there was no evidence for an association between overall antidepressant prescription and the risk of breast cancer risk [24]. Although controversy exists about whether certain antidepressants reduce tamoxifen's effectiveness on lowering breast cancer recurrence, no increased risk of subsequent breast cancer in women who concurrently used tamoxifen and antidepressants, including paroxetine was observed recently in a large study and no evidence was found that either depression or antidepressant use influences breast cancer risk [25].

The use of antidepressants and the occurrence of oral cancer have been studied and selective serotonin reuptake inhibitors and tricyclic antidepressants were associated with a reduced risk of oral cancer [26]. The association between antidepressant use and a decreasing oral cancer risk were demonstrated by both prospective and nested case-control studies [26].

Lithium induces proliferation in the epithelium of renal collecting ducts, however in a nationwide case-control study, use of lithium was not associated with an increased risk of upper urinary tract cancer [17].

Fluoxetine appears to exhibit an apoptotic effect against Hep3B cells through the loss of mitochondrial membrane potential, formation of reactive oxygen species and modulation of mitogen-activated protein kinases activities. In this context, fluoxetine might inhibit cell growth and have an antitumor effect at least in human hepatocellular carcinoma cell lines [27].

Little evidence has found that the use of tricyclic antidepressants increases the risk of non-Hodgkin lymphoma overall or for specific common subtypes of non-Hodgkin lymphoma [28]. Amitriptyline showed potent activity in inducing multiple myeloma cell apoptosis *in vitro*, decreased tumor growth, decreased antiapoptotic Bcl-2 and Mcl-1 in tumor tissues and extended the survival period of multiple myeloma tumor-bearing mice [29].

Nortriptyline induces both intrinsic and extrinsic apoptosis in human and mouse bladder cancer cells and has been discussed a clinically useful chemotherapeutic agent for bladder cancer in humans [30] (see Fig. 2).

In conclusion more controlled studies are needed to show effects of antidepressants on tumor activity and outcome. Concerning the depressive symptomatology there are to our knowledge only two controlled studies comparing different medications in cancer patients i.e. *paroxetine* versus *desipramine* and mirtazapine versus imipramine [31, 32]. In this context there are at the moment no concluding remarks possible concerning the differential influences of antidepressant treatments in cancer patients [31, 32].

In patients with cardiovascular disorders use serotonin reuptake inhibitors

A close, bidirectional relationship exists between depression and cardiovascular disease. Indeed, depression is associated with an increased risk of coronary artery disease, myocardial infarction, congestive heart failure, and isolated systolic hypertension leading to increased mortality and morbidity in patients [33]. However, the rate of rehospitalizations due to cardiovascular events seems to decrease after antidepressant treatment [33] (see Fig. 1).

The comorbidity between depression and cardiovascular disorder includes changes of the central and autonomic nervous, hematologic, neuroendocrine, immune and vascular system. An imbalance between the sympathetic and parasympathetic systems, a loss

of heart rate variability, sympathoadrenal activation, blood viscosity, increase of pro-inflammatory cytokines with concomitant hypothalamic-pituitary-adrenal axis activation, hypercortisolemia, immune system dysregulation, platelet activation and hypercoagulability have been demonstrated in most individuals diagnosed with major depressive disorder [2] (see Fig. 1). Collaborative depression care delivered before cardiovascular disease onset halves the excess risk of cardiovascular disease events among older, depressed patients [34]. Additionally, at least in chronically depressed individuals, an 80% or higher antidepressant adherence lead to a 26% lower risk of hospitalizations in terms of coronary artery disease when compared to patients with a less than 80% adherence [35].

In this context, the prevailing view is, that improvement in depression is necessary to improve cardiovascular outcome. For example, sertraline resulted in greater reductions in depressive symptoms compared to placebo in patients with coronary heart disease and this substance has been evidenced to improve cardiovascular biomarkers and may have a beneficial effect on clinical outcomes as well as on quality of life [36].

However, an improved cardiac status might result in reduced symptoms of depression and reduced symptoms of depression might lead to a better compliance concerning treatment of cardiosvascular symptoms. In this context, patients whose depression improve also exhibit improved cardiovascular outcomes and lower mortality and the beneficial influence of antidepressants on cardiovascular parameters per se is uncertain and not suggested in all studies. In this context, in a study, where antidepressant treatment generated modest symptom reductions, antidepressants did not improve symptoms more than placebo in 2 heart failure trials [37]. Moreover, in patients with heart failure depressive symptoms, not antidepressant therapy predicted event-free survival but depressive patients without antidepressants had a 4.1 times higher risk of death and hospitalization than non-depressed patients on antidepressant treatment [38].

In another study, implementing an antidepressant treatment strategy did not reduce the risk of cardiovascular morbidity and mortality compared to usual care but receiving antidepressant treatment increased survival [39]. It remains unclear whether this represents a direct antidepressant treatment effect or if this is due to associated factors that relate to both receiving depression treatment and mortality, such as patients' intrinsic motivation to care for their health [39]. Among post-coronary artery bypass graft surgery patients with mild to moderate depression in a parallel, double-blind, placebo-controlled trial simvastatin or atorvastatin demonstrated a significant effect for time×treatment interaction on depression severity and treatment with simvastatin showed a superior antidepressant effect when compared to atorvastatin [40]. The examination of data collected from 961 men participating in an Osteoporosis Study showed that documented exposure to statin and aspirin was associated with a reduced likelihood of mayor depression, i.e. among the 210 participants exposed to statins or aspirin, 2.9% in comparison to 5.4% developed de novo major depression 41] (see Fig. 2).

Overall, a decreased risk of developing depression has been reported among statin users [40]. Aside from their lipid-lowering effects, statins are considered immunomodulatory agents and have protective effects against oxidative stress and inflammation which are well known for their association with depression [40] (see Fig. 2).

However, in particular, a reduced risk of myocardial infarction with selective serotonin reuptake inhibitors, particularly fluoxetine was found; however the tricyclic drug lofepramine increased the risk of myocardial infarction in a prospective trial [42]. Antidepressant use and serotonin and norepinephrine reuptake inhibitors were associated with lower baroreflex sensitivity, which was not connected to depressive symptoms per se [43]. Beneficial effects of selective serotonin reuptake inhibitors, i.e. fluvoxamine were demonstrated on ischemia-reperfusion injury, which is in line with the observation that serotonin is activated during ischemia-reperfusion and triggers contractile dysfunction and pathological apoptosis [44, 45]. Paroxetine was discussed a new pharmacological agents for heart failure therapy [46] (see Fig. 2).

Amitriptyline, fluoxetine and tranylcypromine relax rat aorta *in vitro* [47] and duloxetine but not escitalopram significantly increase pulse wave velocity (the gold standard measure for arterial stiffness) in older depressed patients after 12 months of treatment [48].

Patients chronically medicated with serotonin reuptake inhibitors exhibit lower platelet serotonin content and reduced platelet aggregation induced by ADP, collagen and epinephrine which may also explain the increased bleeding risk associated with chronic serotonin reuptake inhibitor treatment as well as the reported beneficial effect of these substances in prevention of recurrent myocardial infarction [49] (see Fig. 2).

Adverse effects precipitated by the tricyclic drug desipramine include prolonged QT intervals, torsade de pointes tachycardia, heart failure, and sudden cardiac death [50]. QT prolongation has been primarily attributed to acute blockade of hERG/I(Kr) currents, i.e. direct hERG channel block, acute reduction of hERG surface expression, chronic disruption of hERG trafficking, and induction of apoptosis 50]. Serotonin-norepinephrine reuptake inhibitors were approved without cardiovascular safety data despite the fact that they raise blood pressure [51].

New generation selective serotonin reuptake inhibitors cause a reduced cardiovascular morbidity and mortality, which may again be related to serotonin platelet abnormalities in depressed patients that are effectively treated [51]. Indeed, fluoxetine, paroxetine, sertraline and citalopram are not only considered to be free from the cardiotoxicity of their predecessors but also to function as safe and efficacious agents against depression, platelet activation, atherosclerosis and development and prognosis of coronary heart disease [49]. Also statins showed an antidepressant effect in a systematic review and meta-analysis [52].

In a register-based cohort study in Denmark the incidence of depression after stroke was 25% compared with 7.8% in the control population [53]. Depressed individuals, especially those with new onset, had increased all-cause mortality, for natural and unnatural causes of death [53]. On the contrary, a matched cohort study in 5.015 subjects showed that patients with a depressive episode had significantly higher rates of stroke (4.3% vs. 2.8%9 [54]. Patients with depression are at greater risk of developing a pathophysiological constitution that may in turn lead to stroke [54]. In addition, both depressive symptoms and taking antidepressant medications are associated with higher risk of stroke [54]. In a matched cohort study patients with a major depressive episode had significantly higher rates of stroke during the nine year follow up period. Greater severity of depression, but not greater use of antidepressants, preceded the occurrence of stroke [54].

In this context, retrospective studies where the use of antidepressants is associated with a higher risk of stroke are difficult to be interpreted. Example given, the use of tricyclic antidepressants, but not serotonin uptake inhibitors or other antidepressants was associated with an increased risk of stroke recurrence. However tricyclic antidepressants are normally used in clinical practice in more severe depressive states than serotonin reuptake inhibitors. Therefore the severity of depression rather than the antidepressant itself might count for stroke recurrence in these patients. This might be in line with the fact that recurrent stroke is particularly elevated when the tricyclic antidepressant treatment is abruptly cessated [55 . Furthermore, all-cause mortality but not the risk of stroke recurrence was higher in patients with stroke and controls treated with benzodiazepines, antidepressants and antipsychotics than in their untreated counterparts [56].

In patients with chronic heart failure and depression, 18 months of treatment with escitalopram compared with placebo did not significantly reduce all-cause mortality or hospitalization, and there was no significant improvement in depression. These findings do not support the use of escitalopram in patients with chronic systolic heart failure and depression [57]. In conclusion, a successful treatment of depressive symptoms per se might reduce the risk of recurrent stroke rather than the antidepressant use itself. In this context, treatment with antidepressants seems to also decrease the risk of developing dementia, i.e. veterans who developed dementia were treated with antidepressants for a significantly shorter duration than matched veterans who did not develop dementia [58].

In conclusion, in patients with cardiovascular disorders tricyclic antidepressants have been proved to show unfavorable side effects, increase the risk of myacardial infarction and lead to arrhythmia and cardiac arrest [59]. However, SSRI seem to have less serious side effects but citalopram and escitalopram may lead to changes of the QT-interval and torsades de pointes [60].

In patients with diabetes use serotonin reuptake inhibitors

Diabetes and insulin resistance are associated with altered brain imaging, depression, and increased rates of age-related cognitive impairment. However, metabolic dysregulation influences brain function and disturbances in peripheral glucose regulation might be associated with cognitive impairment and depressed mood [2, 61] (see Fig. 1). Depression is highly associated with obesity, metabolic syndrome and type-2 diabetes [2, 62-64] and it has even been discussed to classify depression as metabolic syndrome type II [2, 65]. The presence of depressive symptoms is documented in 12.8–29% of males and 23.8–30.5% of females with newly diagnosed diabetes. Diabetes has in turn been shown to affect the incidence of depression [2, 65] and depressive symptoms are predictive of poor glycemic control in type 2 diabetes mellitus patients [2, 66] (see Fig. 1). The occurrence of depression was found to precede the onset of diabetes and was hypothesized to be associated with inherited inter-related insufficiency of the peripheral and central insulin receptors [67].

A number of epidemiological studies have established a link between insulin resistance and the prevalence of depression. In a retrospective study in 923.024 patients an association between hypoglycemic events and depression has been observed in patients with diabetes mellitus, i.e. patients reporting hypoglycemic events had 78% higher odds of experiencing depression than patients without hypoglycemic events [68].

Selective serotonin reuptake inhibitors are recommended if possible to treat a depression among patients with diabetes [69] (see Fig. 2). Antidepressant treatment in patients with diabetes and depressive symptoms showed a reduction in depressive symptoms after treatment with an antidepressant in the acute as well as during maintenance phase [69]. Indeed, the depression improvement had a favourable effect on glycaemic control that was weight independent [69].

A brain-specific knockout of the insulin receptor leads to increased levels of monoamine oxidase A and B leading to increased dopamine turnover in these areas as a direct consequence of loss of insulin signalling [70]. Thus, insulin resistance in brain induces mitochondrial and dopaminergic dysfunction leading to anxiety and depressive-like behaviors, demonstrating a potential molecular link between central insulin resistance and behavioral disorders [70]. Indeed, selective serotonin reuptake inhibitors, i.e. paroxetine, fluoxetine or sertraline inhibit dose-dependent insulin-induced Tyr phosphorylation of insulin receptor substrate 2 protein and the activation of its downstream targets Akt and the ribosomal protein S6 kinase-1, which correlated with a rapid dephosphorylation and activation of the insulin receptor substrate kinase GSK3-beta [71]. Therefore an inhibition of the insulin secretion by serotonin reuptake inhibitors has been suggested and that these drugs might accelerate the transition from an insulin-resistant state to overt diabetes [71].

Diabetes related vascular pathology arises from mitochondrial reactive oxygen species generation, which contributes to endothelial dysfunction and diabetic vasculopathy. In a novel cell-based screening approach of known pharmacological compounds paroxetine has been identified a new property as a potent inhibitor of mitochondrial reactive oxygen species generation [72].

Improvement in depression scores was associated with improvement in biomarkers of insulin resistance, i.e. oral glucose tolerance test and fasting plasma glucose [73] (see Fig. 1).

Selective agonists of the nuclear transcription factor peroxisome proliferator-activated receptor-gamma are used for the treatment of type-2 diabetes. In a recent metaanalyses

resulting from 4 open-label trials and 4 randomized controlled trials in 448 patients peroxisome proliferator-activated receptor-gamma agonists have antidepressant effects in the 4 open-label studies and in 3 out of 4 RCT [73]. Pioglitazone, either alone or as add-on therapy to conventional treatments, could induce remission of depression, suggesting that drugs with peroxisome proliferator-activated receptor-gamma agonist properties may be true and clinically relevant antidepressants, even in patients without metabolic comorbidities, improving depression with mechanisms largely unrelated to its insulin-sensitizing action [72, 74].

Dicholine succinate is a sensitizer of the neuronal insulin receptor and was shown to stimulate insulin-dependent H2O2 production of the mitochondrial respiratory chain leading to an enhancement of insulin receptor autophosphorylation in neurons. It has an antidepressant-like effect, which might be mediated via the up-regulation of hippocampal expression of insulin growth factor 2, and implicate the neuronal insulin receptor in the pathogenesis of stress-induced depressive syndrome [69].

In a double-blind, placebo-controlled study of 1.496 obese or overweight participants with dyslipidemia and/or hypertension naltrexone plus bupropion or placebo were combined to treat obesity for up to 56 weeks [75]. A significantly greater weight loss was observed with naltrexone/bupropion versus placebo at week 28 and week 56. The treatment moreover produced greater improvements in various cardiometabolic risk markers, participant-reported weight-related quality of life, and control of eating [75].

In conclusion, selective serotonin reuptake inhibitors are recommended if possible to treat a depression among patients with diabetes and antidiabetic medications have been shown to induce remission of depression.

Treat inflammation in depression

Repetitive stressfull experiences lead to a crosstalk between inflammatory pathways and neurocircuits in the brain and result in behavioral responses, such as avoidance and alarm, which are likely to have provided early humans with an evolutionary advantage in their interactions with pathogens and predators [76]. Stressfull interactions in modern times are causal factors for depression, however they are nowadays usually not connected with bodily harm. However, circuits between inflammation and brain appear to drive the development of depression and may contribute to non-responsiveness to current antidepressant therapies [76]. Acutely, inflammatory cytokine administration or activation of the innate immune system produces adaptive behavioral responses that promote conservation of energy to combat infection or recovery from injury. In prolonged stress conditions and depression, proinflammatory cytokines activate the hypothalamic-pituitary-adrenal axis, increase cortisol synthesis, damage neuronal networks and activate peripheral macrophages and central microglia, leading to a dysfunctional endocrine and immune system. Thereby oxidative stress and the neurotoxic N-methyl-D-aspartate glutamate agonist quinolinic acid are increased and contribute to neurodegeneration, which characterises depression particularly in late life [76].

In depression proinflammatory activation of monocytes and macrophages and increased serum levels of proinflammatory cytokines have been confirmed. Furthermore, inflammatory cytokines may serve as mediators of both environmental (e.g. childhood trauma, obesity, stress, and poor sleep) and genetic (functional gene polymorphisms) factors that contribute to depression's development. Additionally, potential therapeutic strategies that target inflammatory cytokine signaling or the consequences of cytokines on neurotransmitter systems in the brain to prevent or reverse cytokine effects on behavior are discussed. As also seen in other stress-induced conditions, i.e. myocardial infarction, coronary heart disease and stroke; pro-inflammatory cytokines, such as tumor necrosis factor alpha, interleukin-1 and interleukin-6 stimulate central serotonin neurotransmission

and are over-expressed in depression, which has been again linked with hypothalamic-pituitary-adrenal axis hyperactivity [44] (see Fig. 1).

Interestingly, a special dietary pattern was related to plasma levels of inflammatory markers (C-reactive protein, interleukin-6, tumor necrosis factor α receptor 2) and in a prospective analysis of the relationship of this pattern and depression risk among 43.685 women without depression at baseline relative risks for the strict definition and for the broader definition of depression were both significanty increased (see Fig. 1). Therefore, the inflammatory dietary pattern is associated with a higher depression risk and seems to be influenced by nutritional habits. This finding suggests that chronic inflammation may underlie the association between diet and depression [77] (see Fig. 1).

In overall, depressed patients with chronic heart failure show significantly elevated immune parameters, i.e. interleukin-2, -4, -6, interferon-γ, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 beta and tumor necrosis factor alpha which predict greater severity of depressive symptoms [78].

Tumour necrosis factor alpha is increased in depression and clinical-trial evidence indicates that blocking peripheral tumour necrosis factor alpha has some antidepressant efficacy. In rodents, a recent study adds significantly to the evidence that both peripheral and brain region-specific increases in tumour necrosis factor alpha lead to both sickness and depression- and anxiety disorder-relevant behavior and do so via different pathways 79]. Abnormalities in Toll-like receptor expression (TLR1-9) in depression have been observed in peripheral blood mononuclear cells and postmortem brains of depressed and suicidal patients [80]. The expression of TLR3, TLR4, TLR5, TLR7, TLR8 and TLR9 is elevated in depressed patients and antidepressant treatment completely normalizes TLR3, TLR5, TLR7, TLR8 and TLR9 levels, whereas TLR1, TLR2, TLR4, and TLR6 are decreased to below normal levels[75]. Stress and depression were reported to increase leukocyte and neutrophil counts and to decrease lymphocyte count [81]. Increased production of the main proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha and of acute phase reactants may play a role in the etiopathogenesis of depression[81]. In major depressed unmedicated patients, significant differences were identified in the neutrophil-lymphocyte ratio, neutrophil count, lymphocyte percentage, and leukocyte values of the patient group when compared with the control group [81]. The counterparts of macrophages in the central nervous system are microglia, which detect and subsequently clear microbial pathogens and injured tissue [82]. They defend again pathogenic organisms and clear and repair damaged tissue [82]. Their defence again pathogenic organisms can be active by alcohol, viruses, vaccination, bacterial membrane components and long-chain saturated fatty acids, which again can lead to depressive symptomatology [82].

However, higher levels of interleukin-6 and CRP predict depressive symptoms at a 5-year follow-up, i.e. a positive association was found between baseline levels of interleukin-6 and CRP and persistence of depressive symptoms over 5 years [83].

A recent metaanalysis included 6262 patients with depression treated with anti-inflammatory substances and showed a beneficial overall effect on depressive symptoms [84] (see Fig. 2).

Longterm interferon-alpha therapy can cause wide-ranging psychiatric side-effects from fatigue, insomnia, anxiety to full-blown depression [85]. Nonsteroidal anti-inflammatory drugs were associated with a better antidepressant effect in general, with 9 of 10 trials favoring NSAIDs, whereas a statistical trend was observed favoring cytokine inhibitors among 4 studies, but the results remained heterogeneous [84]. All randomized studies emphasized the adjunctive antidepressant effects of celecoxib within the first 6 to 8 weeks of antidepressant treatment, which was most pronounced among patients with increased proinflammatory markers [84]. In this context, it is possible, that specific subgroups would benefit more from anti-inflammatory intervention, such as patients with low-grade inflammation or comorbid inflammatory diseases [84]. Anti-inflammatory treatment, in particular celecoxib, decreases depressive symptoms without increasing the risk of adverse

effects [84]. Identification of subgroups that could benefit from such treatment might be warranted [84].

Moreover, few studies have investigated the potential antidepressant effects of cytokine inhibitors, suggesting an improvement of depression and specific depressive symptoms, such as anxiety and fatigue among patients with psoriasis or ankylosing spondylitis.

The tetracycline antibiotic minocycline may have antidepressant treatment effects [86]. Recent reviews emphasized aspirin because of a more favorable benefit to risk ratio and potentially better antidepressant effects compared with those of selective COX-2 inhibitors [87]. Also aspirin has been associated with additional antidepressant treatment effects, even at low doses [88]. In a meta-analysis of all double-blind, randomized, placebo controlled clinical trials conducted in subjects with depression statins as an adjuvant therapy to antidepressant treatment (i.e. lovastatin, atorvastatin, and simvastatin. largely improved depressive symptoms as assessed by the HDRS [89]. Adjunctive treatment with L-methylfolate calcium significantly improves tumour necrosis factor alpha, interleukin-8, interleukin-6, CRP and leptin levels and treatment outcomes in patients with major depressive disorder [58]. In eight RCTs adjunctive nonsteroidal anti-inflammatory drugs, omega-3 polyunsaturated fatty acids, N-acetylcysteine and pioglitazone have been tested in the treatment of bipolar disorder and show a moderate and statistically significant antidepressant effect [90]. For a number of agents with immunmodulatory properties, i.e. nonsteroidal anti-inflammatory drugs, cytokine inhibitors, ketamine, polyunsaturated fatty acids, statins and curcumin clinical trials showed successful treatment of depression [91]. In a 25% random sample of the Danish population effectiveness and safety measures were compared between periods of SSRI use only and periods of combined SSRI and NSAID or paracetamol use by applying Cox regression [92]. Concomitant NSAID use increased the risk of any psychiatric contact and with depression whereas low-dose acetylsalicylic acid and ibuprofen reduced the risk of psychiatric contact in general and with depression [92].

Synthetic cortisol compounds have shown acute antidepressant effects but because of cortisol's various effects, these results cannot exclusively be ascribed to an anti-inflammatory effect [93, 94]. Modulation of the mineralocorticoid receptor [95] also improved the effects of antidepressants in randomized, placebo-controlled trials.

The anti-inflammatory action of antidepressants mainly results from their direct interaction with immune cells and from changes in the concentration and the relations of neurotransmitters sensed by these cells [96]. Macrophages are one of the leading cell populations involved in drug-mediated immune effects of antidepressants, which can alleviate chronic inflammation in subjects with depression and in individuals not suffering from depression [90]. Moreover, antidepressants act anti-microbial and anti-tumor immunity [96].

Indeed, antidepressant treatments (monoamine reuptake inhibitors, PDE4 inhibitors, lithium, valproate, agomelatine, tianeptine) inhibit the microglia and macrophage activation [97]. However, the effects of serotonin reuptake inhibitors on inflammatory response, i.e. fluoxetine treatment at least in the hippocampus and in isolated microglia are dependent of environmental conditions, i.e. enriched conditions seem to increase the expression of pro-inflammatory markers while treatment in a stressful conditions seem to produce anti-inflammatory effects [98].

In this context, a longitudinal association between any antidepressant use, especially tricyclic agents and subsequent CRP was confirmed several cohort studies [99]. In an open-label randomized clinical trial the hypothesis was tested that CRP, a commonly available marker of systemic inflammation, predicts differential response to escitalopram and nortriptyline [100]. Indeed, CRP level at baseline differentially predicted treatment outcome with the two antidepressants which was more favorable with escitalopram, when CRP was low and more favorable with nortriptyline when CRP was rather high [100]. Additionally, an association has been described between a clinical antidepressant response and a decrease in markers of systemic inflammation observed during pharmacotherapy with mirtazapine in

a severely depressed but physically well patient [101]. Also agomelatine reduces CRP levels with associated reduction of depressive symptomatology [102].

Moreover, antidepressant agents bupropion and celecoxib might represent an attractive anti-inflammatory therapeutic strategy for depression [103]. In a randomized, double-blind, placebo-controlled trial sertraline significantly decreased serum level of interleukin-6 [104]. The anti-inflammatory effect of sertraline was independent to its efficacy for depression treatment [104]. Imipramine down-regulates microglial activation, attenuates stress-induced corticosterone and interleukin-6 responses in plasma, decreases the percentage of monocytes and granulocytes in the bone marrow and circulation and abrogates the accumulation of macrophages in the brain [105]. In an inflammation model of depression in mice, escitalopram, but not R-citalopram and reboxetine, increased pro-inflammatory cytokine and tumour necrosis factor alpha and decreased interleukin-10 [106]. This is interesting in the clinical context of a less efficient antidepressant effect of reboxetine and R-citalopram in a recent metaanalysis [107 , which might be due to their absent antiinflammatory properties.

Lithium acts as an anti-inflammatory agent, which can be connected to abnormal activity of GSK-3 beta and microglia activation via constitutive induction of kinin-B1 receptor and reduction of kinin-B2 receptor expression and activity [108].

Heterocyclic antidepressants, i.e. amitriptyline, clomipramine and maprotiline have an important anti-inflammatory role, which is dependent on the modulation of neutrophil migration and mast cell stabilization [109]. A shift in the balance of the inflammation toward an anti-inflammatory state in the hypothalamus i.e. the expression of members of interleukin-18 system may represent a common mechanism of action of both the chronic treatments with fluoxetine and imipramine [110]. The *in vitro* literature on antidepressants shows that some antidepressants, such as clomipramine and fluoxetine, more consistently decrease pro-inflammatory cytokines (interleukin-6, interferon-gamma, tumour necrosis factor alpha, whilst others (mirtazapine and venlafaxine) tend to increase their levels [111] In a metaanalysis data from 35 studies treatment nonresponders had higher baseline inflammation parameters and persistently elevated tumour necrosis factor alpha whereas levels of interleukin-6 decreased during antidepressant treatment [112].

Ketamine, a NMDA antagonist, exerts immediate antidepressant effects at subanaesthetic doses and possesses analgesic and anti-inflammatory activities. Ketamine reduces licking times in neurogenic and inflammatory phases of paw oedema; oedema volumes were reduced by up to 50% in mice, respectively. While lithium caused no significant effect, ketamine also decreased tumour necrosis factor alpha, iNOS, COX-2 and GSK3 immunostainings in oedematous paws [113]. Fluoxetine and citalopram decrease the release of the amino acids glutamate and d-serine from activated microglia [114]. Venlafaxine and eicosapentanoic acid act anti-inflammatory as venlafaxine decreases interleukin-6, interleukin-8 and interferon gamma inducible protein and eicosapentanoic acid decreases the levels of interleukin-6, interleukin-15, interleukin-1RA and interferon gamma inducible protein. These effects were associated with a corresponding decrease in nuclear factor κB activity [115]. Unexpectedly, sertraline and docosahexaenoic acid had pro-inflammatory effects, with sertraline increasing interferon alpha and interleukin-6 and docosahexaenoic acid increasing interleukin-15, interleukin-1RA, interferon alpha, and interleukin-6, though these changes were also associated with a decrease in nuclear factor kB activity, suggesting distinct modes of action. Agomelatine and moclobemide had no effect on interleukin-6 secretion [109].

Also lithium exerts effects on pro- and anti-inflammatory mediators [116], i.e. lithium exerts anti-inflammatory effects (e.g., suppression of cyclooxygenase-2 expression, inhibition of interleukin-1beta and tumor necrosis factor-α production, and enhancement of interleukin-2 and interleukin-10 synthesis). Nevertheless, there is a large body of data which indicates that under certain experimental conditions lithium also exhibits pro-inflammatory properties (e.g., induction of interleukin-4, interleukin-6 and other pro-inflammatory cytokines synthesis) 116].

In the treatment of dementia and depression think about lithium

In a recent meta-analytic evaluation diagnosis of depression was shown to be a risk factor of Alzheimers Dementia [117]. A recent review draws attention to the paucity of research and evidence in the area of antidepressant treatment in patients with dementia accompanied by depressive symptoms [118]. In this cochrane based review only four studies were included, where the effectivity of antidepressant therapy was tested and two of these investigated the properties of drugs not commonly used in this population. Only two studies used selective serotonin reuptake inhibitors and produced two significant differences in favour of treatment, however the tolerability of antidepressant treatment was weak [119, 120]. In a recent review investigating refractory depression in the elderly, the only treatment for which there was replicated evidence was lithium augmentation [121]. Moreover, lithium might be associated with a reduction in dementia risk and in the risk of cancer [122, 123] (see Fig. 2). Interestingly, a recent metaanalysis suggests that lithium treatment may have beneficial effects on cognitive performance in subjects with mild cognitive impairment and Alzheimers Disease [124].

In terms of comorbidity of depression and dementia anticholinergic antidepressants should not be used as delirium and cognitive deterioration might be increased. Positive effects of SSRI have been shown for behavioural distrubances in dementia 125]. A sufficient treatment of depression in patients with comorbid dementia can have a positive influence on life quality and cognotive functions [126, 127]. In terms of antidepressant use, a positive effect on cognition has to be questioned, i.e. treatment with sertraline in patients with Alzheimers Disease is not associated with greater improvement in cognition at week 24 than treatment with placebo [128]. Cognitive status does not appear to be impacted by short-term pharmacotherapy, at least in patients treated with SSRI and SNRI [129]. Given this potential risk and the myriad of other well-known adverse effects (i.e. constipation, blurred vision, urinary retention, and delirium) associated with anticholinergic medications, it is prudent to minimize use of these medications and consider alternatives when possible as shown in a recent review [130], However, in this review paroxetine as a highly anticholinergic selective serotonin reuptake inhibitor antidepressant did not increase the risk for dementia when compared with other SSRIs [130]. In the clinical context benzodiazepine use has been associated with an increased risk of dementia, however a recent case control study in 26,459 patients aged ≥65 years with newly diagnosed Alzheimer's disease, long-term use of benzodiazepines was not associated with an increased risk of developing Alzheimer's disease [131 . In conclusion concerning the use of antidepressants in the treatment of dementia an acceptability analysis showed that SSRIs were generally well tolerated but results also suggest that there is insufficient evidence to reject the null hypothesis of no differences in efficacy between SSRIs and placebo in the treatment of depression in dementia [132].

Conclusion

Depression has been confirmed as a heterogeneous disorder with a subgroup of patients suffering from low-grade chronic inflammation, metabolic disturbances and cardiovascular risk profiles which are frequently resistant to traditional antidepressant treatment. A „depressive“ lifestyle might be connected with bad nutritional habits, low exercise, stress, no sleep and a traumatizing environment. This again might lead to low grade inflammation, increased stress hormones to downregulate inflammation and increased risk of diabetes and cardiovascular disease. Fig. 1 shows the pathophysiologic cascade of depression revisited with an exorbitant potential for prohylactic measures, i.e. diet, coping style and exercise, as established also in diabetes and cardiovascular research. In this context, however, at the moment, it is unclear whether individual differences in levels of corresponding biomarkers

could help match patients to drug treatments that are most likely to be beneficial. In Fig. 2 an attempt is made to include actual findings in a hypothetical but pragmatic clinical intervention strategy.

In future, studies and treatment guidelines are needed to compare the outcome of patients regarding combined interdisciplinar treatment strategies in the context of their comorbidity and to identify those depressed patients who could benefit from drugs acting through inflammatory, cardiosvascular and metabolic pathways.

Disclosure Statement

Nothing to delare.

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