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Statins in depression: a repurposed medical treatment can provide novel insights in mental health

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ABSTRACT

Depression has a large burden, but the development of new drugs for its treatment has proved difficult. Progresses in neuroscience have highlighted several physiopathological pathways, notably inflammatory and metabolic ones, likely involved in the genesis of depressive symptoms. A novel strategy proposes to repurpose established medical treatments of known safety and to investigate their potential antidepressant activity. Among numerous candidates, growing evidence suggests that statins may have a positive role in the treatment of depressive disorders, although some have raised concerns about possible depressogenic effects of these widely prescribed medications. This narrative review summarises relevant findings from translational studies implicating many interconnected neurobiological and neuropsychological, cardiovascular, endocrine-metabolic, and immunological mechanisms by which statins could influence mood. Also, the most recent clinical investigations on the effects of statins in depression are presented. Overall, the use of statins for the treatment of depressive symptoms cannot be recommended based on the available literature, though this might change as several larger, methodologically robust studies are being conducted. Nevertheless, statins can already be acknowledged as a driver of innovation in mental health, as they provide a novel perspective to the physical health of people with depression and for the development of more precise antidepressant treatments.

Introduction

Depression is a common disabling disorder (Demyttenaere & Van Duppen, 2019; James et al., 2018) for which current management strategies, including psychotherapy and pharmacotherapy (Cuijpers et al., 2020; Furukawa et al., 2021), are not satisfactory (Malhi et al., 2020). While about half of patients with depressive illness respond to first-line antidepressant medication, one-third still suffer from impairing symptoms after four treatment steps over one year (Rush et al., 2006). Concordance with treatment is a further significant issue (Solmi et al., 2021), with more than one-quarter discontinuing antidepressants due to any cause or because of intolerable side-effects (Cipriani et al., 2018).

Most licenced antidepressants, which work in the main by modulating monoaminergic neurotransmission, are characterised by a delayed therapeutic onset (Harmer et al., 2017), further complicating the effective management of this condition (Malhi et al., 2020).

Overall, there is a compelling need to identify novel molecular targets in depression and thus new antidepressants that can act on them (Jarończyk & Walory, 2022), particularly with a view to tailoring treatment to the individual patient (Maj et al., 2020). Regrettably, clinical research and drug development in this area is challenging (Rush et al., 2022), and indeed several pharmaceutical companies have disinvested from it (Ciccocioppo, 2017). An innovative and promising approach proposes instead to repurpose existing medications with a well-defined safety profile and capable of targeting emerging physiopathological pathways implicated in depression (Berk & Nierenberg, 2015; Ebada, 2017; Mohammad Sadeghi et al., 2021), similarly to what has been recently advocated for bipolar illness (Bartoli et al., 2021).

Currently, the conceptual neurobiological framework surrounding depressive disorders encompasses a variety of mechanisms including deeply interconnected neurobiological and neuropsychological,

endocrine-metabolic, cardiovascular, and immunological systems (Bot et al., 2020; Caspani et al., 2021; Chavez-Castillo et al., 2020; Guerreiro Costa et al., 2022; Jones et al., 2021; Kokkeler et al., 2022). In this context, pre-clinical and clinical studies consistently show that the 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors, or statins, are intriguing candidates for repurposing in neuropsychiatric disorders (Avan et al., 2021; Fernandes et al., 2021; Fracassi et al., 2019; Rahola, 2012; Tao et al., 2021), and especially in depression (Covington et al., 2010; Fabbri et al., 2021; Le-Niculescu et al., 2021; Maes et al., 2012; Mohammad Sadeghi et al., 2021; So et al., 2019).

Statins are a class of lipid-lowering drugs, among the most widely prescribed worldwide (Simons, 2003), which have been used for several decades to treat and prevent cardiovascular, cerebrovascular, and metabolic disorders (Sizar et al., 2022). Their primary mechanism of action involves the competitive, reversible antagonism of liver HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis (Endo et al., 1976). However, statins are described as possessing "pleiotropic effects" (Yu & Liao, 2022), of which the anti-inflammatory actions are best characterised today (Zeiser, 2018).

Statins express their pleiotropic activities differentially, based on both their potency and lipophilicity/hydrophilicity (Irwin et al., 2020): their variable strength and neural entry/efflux emphasise the need for these molecules to be considered individually with respect to their pharmacological activity in the central nervous system (CNS) (McFarland et al., 2014). Statins can affect brain function both directly, via local neurobiological and neuropsychological effects, and indirectly, by influencing deeply interconnected systems (i.e. endocrine-metabolic, cardiovascular, immunological) that ultimately have an impact on mental processes (Farooqui et al., 2007; Fracassi et al., 2019). The most recent evidence from basic science (Walker et al., 2021) and clinical research (Hayes et al., 2019; Kim et al., 2019) indicates that statins may play a role in the treatment of neuropsychiatric syndromes, particularly in the context of affective disorders such as depression (Bortolato et al., 2016; De Giorgi et al., 2021).

Translational evidence for statins in depression

It has been shown that statin administration can improve depressive-like behaviour in animals (Kilic et al., 2010). More intriguingly, several lines of evidence from translational investigations *in vitro*, animal, and human models have provided valuable information not only about the putative antidepressant effect of statins (i.e. forward findings), but also on some of those neurobiological and neuropsychological, cardiovascular, endocrine-metabolic, and immunological processes underpinning the physiopathology of depressive disorders (i.e. backward findings) (Figure 1).

Statins can affect brain biology through their activity on neurotransmission and neurogenesis/neuroprotective processes. Though several neurotransmitters have been involved (Kosowski et al., 2021), most of the evidence concerns serotonin (5-HT) transmission, suggesting that antidepressant effect of statins may be due to their capacity to increase availability of the serotonin precursor, tryptophan (Kilic et al., 2012) and overall hippocampal serotonin levels (ElBatsh, 2015), while also showing 5-hydroxytryptamine
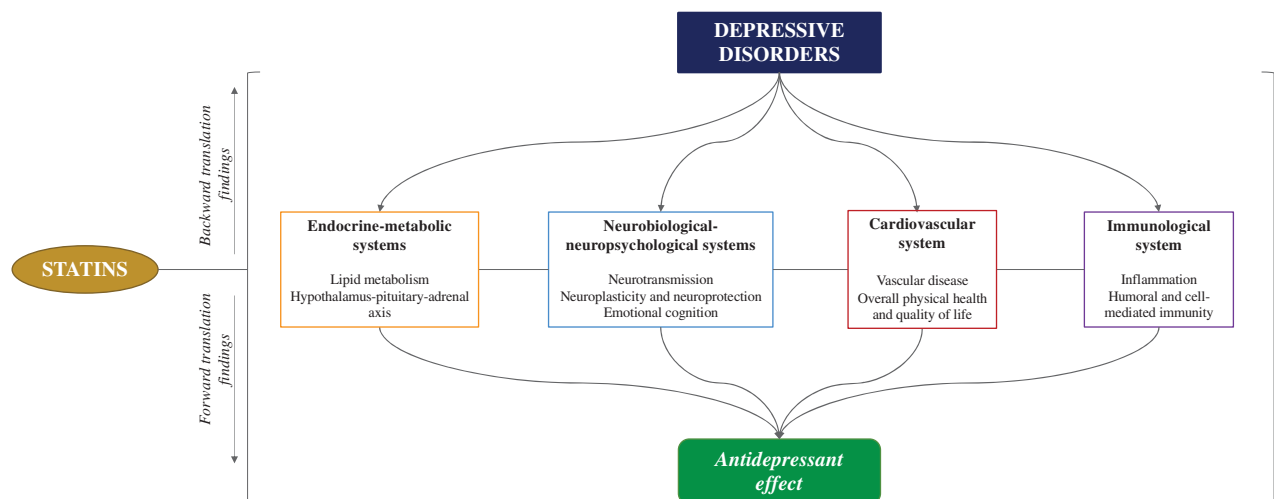

Figure 1. Statins as a probe for depressive disorders physiopathology and antidepressant effect.

receptor (5HT$_{1A}$, 5HT$_{2A/C}$, and 5HT$_3$) antagonism (Ludka et al., 2014; Nothdurfter et al., 2010; Shrivastava et al., 2010). Further, selective serotonin reuptake inhibitors (SSRIs) pharmacodynamics (Kilic et al., 2012; Ludka et al., 2014; Renshaw et al., 2009; Santos et al., 2012) and pharmacokinetics (Al-Asmari et al., 2017; Bhattarai et al., 2017; Li et al., 2017) appear modulated by statin administration.

Statins also affect non-monoaminergic pathways, including N-methyl-D-aspartate (NMDA) receptor antagonism (da Cruz et al., 2017; Kilic et al., 2012; Ludka et al., 2013; Wang et al., 2009; Yan et al., 2011), which is implicated in the effects of ketamine on mood (Zanos & Gould, 2018). The antidepressant effects of statins have also been associated with induction of neuroprotective pathways (Eisel et al., 2010; Ludka et al., 2016) and decreased neuronal damage due to glutamate excitotoxicity, inflammation, and oxidative stress (Ludka et al., 2013, 2017b), as well as increased neurogenesis through brain-derived neurotrophic factor (BDNF) (Binder et al., 2015; Ludka et al., 2013, 2017a; Tang et al., 2020; Tsai, 2007). Besides these diverse neurobiological actions, recent human studies have shown that statins can influence neuropsychological functions such as emotional processing (De Giorgi et al., 2021, 2022; Gillespie et al., 2022), which have been robustly linked to depression and its treatment (Godlewska & Harmer, 2021).

As mentioned, statins are primarily used in the context of cardiovascular disorders: it has been proposed that their ability to reduce thrombogenesis and improve cerebral blood flow in animals (Sheets et al., 2016) and humans (Massardo et al., 2020; 2022; van Agtmaal et al., 2017) might lead to an improvement in cognitive and emotional functioning, as well as in patients' overall physical health and quality of life (Downs et al., 1993; Yang et al., 2003) – all elements associated with fewer depressive onsets, especially in the elderly (Taylor et al., 2013).

The metabolic effect of statins on systemic lipids are well established, but their consequences on mood regulation less so. Some studies have found that cholesterol and related metabolites can modulate statins' reduction of depressive- and anxiety-like behaviour in rats (Can et al., 2012; Segatto et al., 2014), while others have failed to identify such association (Citraro et al., 2014). In humans, excessively low concentrations of blood cholesterol correlate with the onset of depressive episodes, but when cholesterol-lowering is achieved via statins, such association does not persist (Persons et al., 2016). On the other hand, certain antidepressants and antipsychotics with antidepressant

activity have been associated with higher lipid levels (Vancampfort et al., 2014). Statins are also capable of expressing an endocrine effect on the hypothalamic-pituitary-adrenal (HPA) axis and cortisol, thus controlling stress (Kumar et al., 2012; Lin et al., 2014) and immune responses (ElBatsh, 2015; Sheets et al., 2016) that seem to play a significant role in depression (Pellosmaa et al., 2015; Pellosmaa & Dougall, 2016).

Indeed, the immunological effects of statins in depression, especially via anti-inflammatory mechanisms, are the most investigated, since exaggerated or overactive inflammation appears crucial in at least certain subtypes of depressive disorders (Miller et al., 2017). Numerous studies have shown that statins can reduce circulating pro-inflammatory cytokines, such as interleukins (IL), tumour necrosis factor (TNF)-α, and C-reactive protein (CRP) in both animals (Hai-Na et al., 2020; Lim et al., 2017; Menze et al., 2021; Sheets et al., 2016; Wu et al., 2019; Yu et al., 2019; Zhang et al., 2017) and humans (Kang et al., 2016; Kim et al., 2018; Lesperance et al., 2004; Ma et al., 2016), and this anti-inflammatory effect also correlates with their antidepressant activity. Non-inflammatory mechanisms, pertaining to humoral and cellular immunity, preliminarily indicate that statins might affect tryptophan metabolism through these less studied processes (Neurauter et al., 2003; Wirleitner et al., 2003, 2004).

Overall, translational evidence that uses statins as a probe for depression and its treatment highlights intriguing avenues for further research on largely interconnected neurobiological and neuropsychological, cardiovascular, endocrine-metabolic, and immunological systems. However, translation of findings from *in vitro*, animal, and indeed human studies to medical practice remains particularly challenging in psychiatry (Nestler & Hyman, 2010); therefore we now provide an overview of the latest studies exploring the clinical effects of statins in depression.

Clinical evidence for statins in depression

Early evidence had raised concerns about potential connections between statin use, low cholesterol, increased mortality due to suicide, and depressive symptoms (Muldoon et al., 1990; Shin et al., 2008). Consistently, meta-analytic data suggested a possible relationship between lower lipid levels and suicidality in depression (Wu et al., 2016), though not in bipolar depression (Bartoli et al., 2017), perhaps suggesting a possible role of clinical and biochemical confounding

Table 1. Clinical studies investigating the effect of statins in depression.

	Positive effect	No effect	Negative effect
Meta-analyses of randomised controlled trials	5	3	-
Clinical trials	7	14	1
Meta-analyses of observational studies	1	2	-
Observational studies	24	18	7
Case series	-	-	6
TOTAL	37	37	14

Legend. Data represent the number of studies showing either a positive, negative, or no effect per each study category; shape size is proportional to the $\log_{10}$ for the number of studies.

factors underlying such associations (Bartoli et al., 2017).

More recently, many clinical studies have directly investigated the potential effect of statins on depressive symptoms. Previous work from our group had summarised the existing evidence for this topic (De Giorgi et al., 2021); an updated search on the 8th of April 2022 (i.e. one year later) has retrieved further 16 records, for a current total of 88 studies. A graphic display of the beneficial, null, or harmful outcomes on depression observed for statin use, according to study design, is in Table 1. The most recent, largest studies are described below.

Clinical trials and their meta-analyses

The majority of the twenty-two clinical trials have been variably included in the eight available meta-analyses. Two pair-wise meta-analyses published in the same year (Köhler-Forsberg et al., 2019; Yatham et al., 2019) comprised distinct subsets of randomised controlled trials (RCTs), despite similar inclusion criteria, yet reached the same conclusion: statins appeared to have a small to moderate positive effect on depressive symptoms [$N_{\text{range}} = 1,576–2,517$; standardised mean difference $(SMD)_{\text{range}} = -0.31$ to -0.26; 95% confidence interval $(CI)_{\text{range}} = -0.52$ to -0.09].

Two network meta-analyses, also containing a pairwise component, respectively compared statins against each other (Lee et al., 2021a) and against other drugs with anti-inflammatory properties (Hang et al., 2021). The former involved thirteen RCTs ($N = 2,479$) and

showed that statins were on the whole better than placebo in reducing depressive symptoms [mean difference (MD) $= -0.35$; 95%CI $= -0.59$ to -0.11], with atorvastatin seemingly the most efficacious ($MD_{vs\ placebo} = -3.46$; 95%CI -5.26 to -1.67) (Lee et al., 2021a). The second only included three RCTs ($N =$ not reported) and did not identify any effect on depression [relative risk (RR) $= 0.68$; 95%CI $= 0.38–1.18$] (Hang et al., 2021).

Two more recent pair-wise meta-analyses, which expand on a subgroup analysis of the earlier work by Yatham et al. (2019), may explain the reason behind these discrepancies: pooled results from trials that had administered statins in add-on to antidepressants in patients diagnosed with a depressive disorder showed a moderate beneficial effect (four RCTs; $N = 238$; SMD $= -0.48$; 95%CI $= -0.74$ to -0.22) of this intervention compared to antidepressants alone (De Giorgi et al., 2021), whereas statins used in monotherapy *versus* placebo in trials including people experiencing depressive symptoms, without a formal diagnosis of depression, appeared ineffective (eleven RCTs; $N = 2,712$; SMD $= -0.18$; 95%CI $= -0.41$ to 0.04) (De Giorgi et al., 2022).

Some clinical trials could not be entered in the quantitative synthesis of the meta-analyses above for a variety of reasons, including lack of usable data or a non-randomised and/or non-controlled design. Notably, these included the only negative crossover RCT, conducted on 120 hyperlipidaemic men aged 35–64 years, for whom simvastatin dispensed for

24 weeks led to a small increase in scores on the Beck Depression Inventory (BDI) (MD = 0.06; 95%CI = 0.01–0.12) compared to placebo (Hyyppä et al., 2003). A trial comparing simvastatin *versus* atorvastatin (i.e. without a placebo arm) in 46 post-coronary artery bypass patients with comorbid mild-to-moderate depression showed that depression scores measured on the Hamilton Depression Rating Scale (HDRS) at 6 weeks were significantly lower in the simvastatin group (MD = 3.63; 95%CI = 0.44–6.51) (Abbasi et al., 2015). A small ($N = 10$), recent RCT randomised participants to either rosuvastatin or placebo plus SSRI: improvements on depression scales (BDI and HDRS) were observed in both groups, and were reportedly larger in those treated with a statin on the BDI (placebo $p = 0.038$; rosuvastatin $p < 0.001$) but not on the HDRS (placebo $p < 0.002$; rosuvastatin $p < 0.001$) (Massardo et al., 2022); however, no test for directly comparing the two groups was performed

Observational studies and their meta-analyses

Several observational studies and their meta-analyses are available, showing more variable results for the effects of statins in depression (positive = 25, none = 20, negative = 7), likely due to different designs and populations, exposures/comparisons, and outcomes of interest. However, compared to interventional trials, observational data retains great value as it can benefit from oftentimes larger unselected study populations and longer follow-ups (Kennedy-Martin et al., 2015).

Neither of the two most recent meta-analyses of observational studies could identify an effect of statins in depression. The larger one included thirteen observational studies over 5,035,070 participants and initially found a positive effect on the odds of depression for statin users [odds ratio (OR) = 0.85; 95%CI = 0.72–0.99], but no association (OR = 0.87; 95%CI = 0.74–1.02) was eventually confirmed when a trim-and-fill analysis, which corrects for publication bias, was employed (Lee et al., 2021b). The other meta-analysis investigated several cardiovascular medications and comprised nineteen observational studies over 178,278 participants on statins, again not finding any association between these drugs and depression (OR = 0.78; 95%CI = 0.57–1.06) (Zhang et al., 2022).

Some recent observational studies were not included in the previous meta-analyses. A historical cohort study over 21 years of prescription data from 497,080 statin users found that these medications decreased the rate of incident depression (trend test for statin prescription = 0.92; 95%CI = 0.92–0.95) (Kessing et al., 2019). Similar results for a larger

sample of 1,149,384 statin users followed for 8 years were seen in an epidemiological investigation using a within-subject design, which showed that presentations to mental health services for depressive episodes were less frequent during periods on statins compared to periods off them [hazard ratio (HR)= 0.91; 95%CI 0.88–0.94] (Molero et al., 2020).

In contrast, two studies highlighted a harmful association between statins and depression. One was conducted on a large nationwide database ($N = 7,481,168$) and observed an overrepresentation of depressive disorders in statin users compared to non-users (OR = 1.22; 95%CI 1.20–1.25), though this association appeared reversed when considering low doses of statins, and worsened in high-dose users (Leutner et al., 2021). Another used a Mendelian randomisation methodology and likewise noted a 12% increase in the odds of depression for people taking statins ($N = 188,000$; 95%CI = 1.04–1.18) (Alghamdi et al., 2018). Interestingly, a propensity-score matched analysis of 193,977 statin users and 193,977 non-users also revealed higher hazards of depression diagnosis in the exposed group (HR = 1.33; 95%CI = 1.31–1.35) followed for a mean 6.8-year, but such association became non-significant when controlled for antidepressant use (Köhler-Forsberg et al., 2019).

Only one earlier study on a cohort of SSRIs users had specifically focussed on the issue of concurrent statin and antidepressant use, yet it reported lower hazards for psychiatric hospital contacts due to depression ($N = 872,216$; HR = 0.64; 95%CI = 0.55–0.75] among those using statins plus SSRIs *versus* SSRIs-only (Köhler et al., 2016). We are currently working on a real-world, primary care-based study comparing statin use against non-use in two cohorts of patients diagnosed with first-episode depression: one including only people initiating for the first time an antidepressant therapy (i.e. statin plus antidepressant *versus* antidepressant alone); the other encompassing all statin users *versus* non-users (De Giorgi et al., 2022). Preliminary analyses show a more positive profile for the combined strategy of statins and antidepressants (unpublished material), which is in line with findings from meta-analyses of clinical trials (De Giorgi et al., 2021, 2022; Yatham et al., 2019), but more definitive evidence is required before drawing any conclusion on the potential augmentative effects of statins on antidepressants.

Statins as a tool for innovation in psychiatry

Based on the translational and clinical findings presented above, the repurposing of statins for depressive disorders seems particularly tempting. These

"old-school" drugs are safe (Collins et al., 2016) and commonly used in today medical practice (Urquhart, 2019), but for mental health researchers and psychiatrists they are novel because they can target underexplored biological pathways implicated in depression while also showing promising signs of efficacy, or at least no harm, in patients with depressive illness. Naturally, the available evidence remains preliminary, and these exciting perspectives must be taken with caution and further investigated (Köhler-Forsberg et al., 2020). While statins may not be the next 'breakthrough' in antidepressant development, nevertheless some interesting implications for research and clinical practice can already be argued.

Implications for research: approaching "precision" in depression

From a translational, "backward" perspective (Figure 1), statins have pleiotropic actions (Yu & Liao, 2022) on a very large number of neurobiological and neuropsychological, endocrine-metabolic, cardiovascular, and immunological processes: the relationship between all these factors and their exact consequences in terms of antidepressant or depressogenic effect may have not been unravelled, but their relevance to depression is strengthened and expands beyond the classic monoamine hypothesis to explain it (Hirschfeld, 2000).

In other words, statins can be used as a dependable, if somewhat unselective probe into the role of factors such as dyslipidaemia (Can et al., 2012; Citraro et al., 2014; Persons et al., 2016; Segatto et al., 2014), HPA axis abnormalities (ElBatsh, 2015; Kumar et al., 2012; Lin et al., 2014; Pellosmaa et al., 2015; Pellosmaa & Dougall, 2016; Sheets et al., 2016), changes in emotional processing (De Giorgi et al., 2021; 2022; Gillespie et al., 2022), or inflammation (Hai-Na et al., 2020; Kang et al., 2016; Kim et al., 2018; Lesperance et al., 2004; Lim et al., 2017; Ma et al., 2016; Menze et al., 2021; Sheets et al., 2016; Wu et al., 2019; Yu et al., 2019; Zhang et al., 2017), as well as some of their interactions, in the physiopathology of depressive disorders. This list is hardly exhaustive: for example, statin therapy has recently been associated with a reduction of gut microbiota dysbiosis and thus systemic inflammation (Vieira-Silva et al., 2020), which in turn seem involved in the onset of depressive symptoms (Eltokhi & Sommer, 2022) and could mediate antidepressant response (McGovern et al., 2019) via the gut-brain axis.

From a translational, "forward" perspective (Figure 1), these factors may become useful, oftentimes easily measurable (e.g. lipid profile, cortisol levels, negative emotional bias, or CRP and other peripheral cytokines) biomarkers that can be utilised in the design of more precise studies for developing new antidepressants or repurposing other medications as such. It is likely that either a deficit or an exaggeration of some, but not all the above mechanisms at the same time would characterise different clinical presentations on a spectrum of depressive disorders requiring treatment(s) addressing those specific dysfunctions (Maj et al., 2020).

Here, statins widespread activities are double-edged, as in practice they would turn into altering certain physiological functions that are not necessarily helpful, or are in fact plainly unhelpful, for eliciting an antidepressant response. An example of this is perhaps observable by comparing the results of those meta-analyses that had suggested a positive effect of statins in people formally diagnosed with a depressive disorder (De Giorgi et al., 2021; Yatham et al., 2019) against those that had found no overall effect of statins on depressive symptoms in heterogenous populations with subclinical depressive symptoms and a variety of underlying medical disorders (De Giorgi et al., 2022; Yatham et al., 2019).

Several physical comorbidities such as hyperlipidaemia (Wee et al., 2016), cardiovascular (Wium-Andersen et al., 2017b) or cerebrovascular (Wium-Andersen et al., 2017a) diseases, neurodegenerative (Sparks et al., 2005) and inflammatory (Kang et al., 2016; Kim et al., 2018) disorders, as well as demographic variables such as age (Berk et al., 2020; Kim et al., 2019; Redlich et al., 2014) and sex (Feng et al., 2010; Pasco et al., 2010; Williams et al., 2016) can likewise present with an array of risk factors for depression, which would relate to a variable antidepressant efficacy for statins. In this respect, statins would not be used directly as a "precision" treatment for individual patients with depression. However, statin studies (Figure 2) may help approaching that by identifying biomarkers that can stratify these subjects according to different subtypes of depressive disorders (Arns et al., 2022).

Then, for example, people whose depression presents with a prominently immunological component, as observed via biomarkers such as elevated peripheral cytokines (Miller et al., 2017), could be targeted with more selective immunomodulatory drugs (Drevets et al., 2022), while others whose symptoms seem associated with interconnected
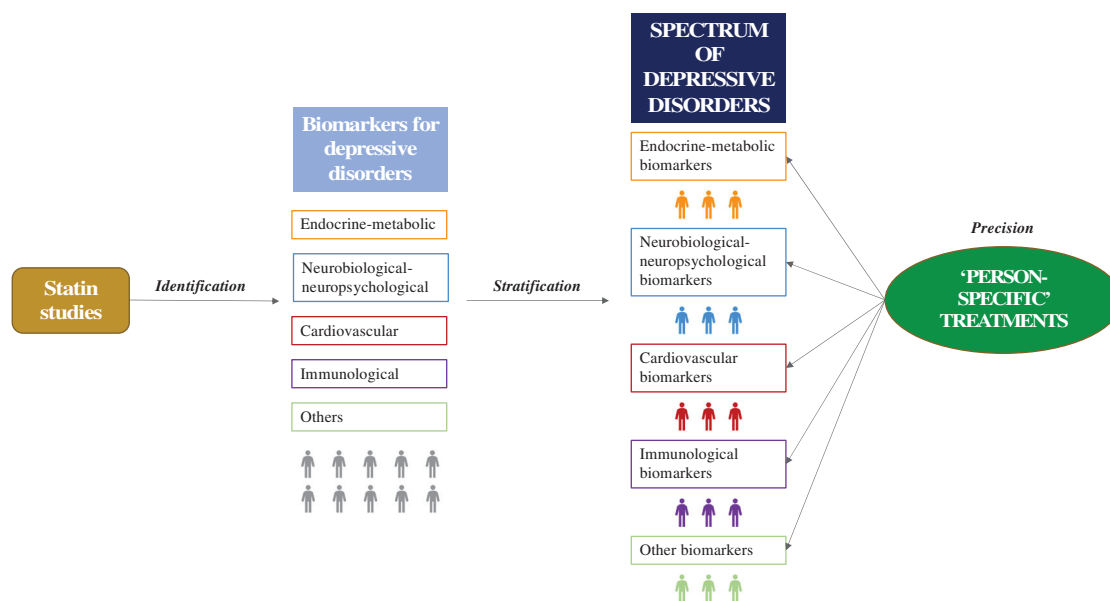
Figure 2. Towards a precision treatment for depressive disorders.

inflammatory and endocrine-metabolic abnormalities, such as obesity, lipid dysregulation, and insulin resistance (Jones et al., 2021; Qiu et al., 2021), may benefit from broader approaches ranging from conventional treatments including diet and exercise (Jacka & Berk, 2013) and statins themselves (De Giorgi et al., 2021), to newer drugs such as glucagon-like peptide-1 (GLP1) receptor agonists (Detka & Głombik, 2021). Ultimately, an integration of advanced data from sources such as multi-omics, neuroimaging, artificial intelligence, and molecular epidemiology and physiology studies will converge towards recognising specific clusters of biomarkers that can lead to precise, person-specific treatments (Fernandes et al., 2017).

Implications for clinical practice: physical health in depression

The scandal of the "mortality gap," mostly due to comorbid physical illness(Momen et al., 2022; Weye et al., 2020), in people with mental disorders including depression is a notorious, much debated topic (Fiorillo & Sartorius, 2021), which has become even more relevant in the context of the Covid-19 pandemic and its aftermath (Fiorillo & Gorwood, 2020). Lifestyle psychosocial interventions have proved useful for improving physical health (Luciano et al., 2021) and reducing mortality (Fiorillo et al., 2019), but several barriers, including concordance with treatment, may hinder their immediate application to patients suffering from depressive symptoms. Adherence to pharmacological treatment, especially antidepressants,

is another significant issue (Dell'Osso et al., 2020) that has been associated with ill-health and mortality in depression (Krivoy et al., 2016).

Overall, interventions aimed at improving the physical health of patients with depressive disorders are under researched and even less frequently applied to clinical practice, but if psychiatry is to fully integrate with modern medicine, it becomes paramount that psychiatrists work confidently at the interplay between physical and mental illness (Fiorillo & Maj, 2018). Here, the use of statins in depression can already provide a clinically meaningful opportunity.

Firstly, in spite of the established physical health benefits (Yebyo et al., 2019) and decrease in all-cause mortality (Gitsels et al., 2021) associated with statin therapy, there are reports of systematic underuse of these medications in patients with depression (Ljung et al., 2021) – precisely those individuals who might benefit the most from their positive cardiometabolic effects (Vancampfort et al., 2017). Secondly, new research has found that statin adherence, concordance with antidepressant treatment, and lower mortality rates independently correlate with each other (Avrahamy et al., 2021). In line with this, preliminary analyses (unpublished material) of our ongoing study (De Giorgi et al., 2022) show that statin use can be associated with both lower antidepressant discontinuations and all-cause mortality, in the absence of any significant adverse events. Nevertheless, it remains possible that a spurious association between the use of medications such as statins and antidepressant efficacy might be partly explained by overall depression

severity and related treatment adherence – despite more recent observational studies having controlled for these potential confounders.

In summary, emerging evidence advises that statin treatment may become a safe and viable strategy to improve both mental and physical health outcomes in patients with depressive disorders, but once again these suggestions must be corroborated by further studies before finding an application to clinical practice.

Conclusion

In this article, we have narratively reviewed the translational and clinical evidence for the effects of statins in depression. On these bases, we have argued that statins may be an instrument that brings novelty to psychiatry research and practice, including some potential implications for developing more precise antidepressant treatments and for better managing the physical health of patients with depressive disorders.

Several clinical and research questions remain unanswered. Do different populations likewise show an antidepressant response to statins? For example, healthy subjects, individuals at-risk for depression, patients with first-episode or treatment-resistant depressive disorders, people with heightened risk due to clinical-demographic characteristics associated to inflammation and dyslipidaemia might be more or less prone to respond to statins (De Giorgi et al., 2021).

Are individual statins capable of expressing distinct influences on mood and anxiety, and at which dosage and length of treatment? In this case, simvastatin's profiling is emerging as superior to other statins (Abbasi et al., 2015; De Giorgi et al., 2021, 2022; Molero et al., 2020; Redlich et al., 2014), but dose- and time-response relationships remain ambiguous. Do statins work better as adjunct to conventional antidepressant, rather than a standalone treatment? The clinical evidence above seems to suggest so (De Giorgi et al., 2021, 2022; Yatham et al., 2019), but the biological and psychological (Al-Asmari et al., 2017; Bhattarai et al., 2017; Kilic et al., 2012; Li et al., 2017; Ludka et al., 2014; Renshaw et al., 2009; Santos et al., 2012) underpinnings of such augmentative effect must be better defined before having any meaningful medical application.

Are the existing outcome measures adequate for detecting the favourable or detrimental consequences of statin use in depression? Scales measuring depressive or anxiety symptoms, neuropsychological tasks, hard outcomes such as mortality, suicidality, and psychiatric hospitalisations: all have the potential to provide clinically and translationally useful insights, but it remains uncertain which one is better tailored to gauge the effects of statins in the context of depressive illness (De Giorgi et al., 2021). Overall, it is likely that many further investigations involving a variety of research designs (i.e. clinical and experimental medicine trials, observational studies) will be required before finding an answer to all these lingering queries.

Disclosure statement

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