Targeting the ferroptosis crosstalk: novel alternative strategies for the treatment of major depressive disorder

Luyao Wang,1,2 Rongyang Xu,1,2 Chengying Huang,2 Guozhong Yi,1 Zhiyong Li,1 Huayang Zhang,2 Rongxu Ye,2 Songtao Qi,1,3 Guanglong Huang,1,3 Shanqiang Qu1,2,3

ABSTRACT
Depression is a major contributor to poor global health and disability, with a recently increasing incidence. Although drug therapy is commonly used to treat depression, conventional antidepressant drugs have several disadvantages, including slow onset, low response rates and severe adverse effects. Therefore, developing effective therapies for depression remains challenging. Although various aetiological theories of depression exist, the underlying mechanisms of depression are complex, and further research is crucial. Moreover, oxidative stress (OS)-induced lipid peroxidation has been demonstrated to trigger ferroptosis. Both OS and ferroptosis are pivotal mechanisms implicated in the pathogenesis of neurological disorders, and investigation of the mediators involved in these processes has emerged as a prominent and active research direction. One previous study revealed that regulatory proteins involved in ferroptosis are implicated in the pathogenesis of depression, and antidepressant drugs could reverse depressive symptoms by inhibiting ferroptosis in vivo, suggesting an important role of ferroptosis in the pathogenesis of depression.

Hence, our current comprehensive review offers an up-to-date perspective on the intricate mechanisms involved, specifically concerning ferroptosis and OS in the context of depression, along with promising prospects for using molecular mediators to target ferroptosis. We delineate the key targets of molecular mediators involved in OS and ferroptosis implicated in depression, most notably reactive oxygen species and iron overload. Considering the pivotal role of OS-induced ferroptosis in the pathogenesis of neurological disorders, delving deeper into the underlying subsequent mechanisms will contribute significantly to the identification of novel therapeutic targets for depression.

INTRODUCTION
Major depressive disorder (MDD) is a psychiatric disorder characterised by persistent low mood, loss of interest, cognitive impairment and loss of appetite, among other symptoms. In recent decades, the incidence of depression in adults has significantly increased due to accumulating pressure from life and work. Data from the National Health and Nutrition Examination Survey in the USA estimates approximately 8.1% of adults experience depression in a given 2-week period, with women (10.4%) almost twice as likely as men (5.5%) to be affected (online supplemental figure 1). MDD affects 16.2% of adults during their lifetime, leading to substantial economic losses and posing a significant health burden on patients. While drug therapy, such as amitriptyline, remains the preferred clinical treatment for MDD, traditional antidepressant drugs have several drawbacks, including slow onset, low response rate and severe adverse effects, suggesting that other molecular mechanisms are involved in the progression of depression. Although the pathophysiology of MDD remains unknown, several underlying mechanisms have been reported. Thus, further exploration of the pathogenesis of MDD and the development of novel potential drugs are necessary.

Previously, MDD was thought to be caused by brain-derived neurotrophic factor disorders and other neurotransmitter alterations; however, recent studies have shown that inflammation and oxidative stress (OS) in the brain are highly related to depression. OS is closely associated with various pathological mechanisms, including neuroinflammation and mitochondrial dysfunction, which are also strongly associated with depression. Inflammation may augment the progression of depression, which further exacerbates inflammation and forms a co-activated state. Additionally, inflammation and depression may share similar aetiological bases, such as OS. OS is caused by the overproduction of reactive oxygen species (ROS) that cannot be eliminated by antioxidant defence systems. ROS homeostasis has a crucial role in regulating the cellular redox balance. Ding et al found that intracellular ROS causes dysfunction of the 5-hydroxytryptamine (5-HT) system in mouse


► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gpsych-2023-101072).

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

1Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

2The Laboratory for Precision Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

3Institute of Brain Disease, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China
Figure 1  (A) Timeline of important affairs in ferroptosis discovery. (B) The role of ferroptosis in the pathological processes of different organs. ACSL4, acyl-CoA synthetase long-chain family member 4; CoQ10, coenzyme Q10; CoQH2, dihydroubiquione; DHODH, dihydroorotate dehydrogenase; FSP, ferroptosis suppressor protein; NADPH, nicotinamide adenine dinucleotide phosphate; PDTACs, photodegradation-targeting chimeras; PROTACs, proteolysis-targeting chimeras; PUFA, polyunsaturated fatty acid; xCT, cystine/glutamate antiporter.

brains by regulating tryptophan hydroxylase-2, eventually leading to depression-like behaviors. Therefore, ROS accumulation associated with ferroptosis may have a significant role in the pathogenesis of MDD.

Ferroptosis was first reported in the 1980s by Bannai et al. After over two decades of development, classical agonists of iron death, erastin and rat sarcoma (RAS)-selective lethal 3 (RSL3), were discovered in 2003 and 2008, respectively; however, it was not until 2012 that Dixon et al identified iron-related death as a distinct form of cell death (figure 1A). In the subsequent decade, research on iron death has gained momentum and has become a highly promising investigational domain. As shown in figure 1B, ferroptosis is responsible for many organ injuries and degenerative pathologies; therefore, inducing or inhibiting ferroptosis is of great significance for ameliorating related diseases. Notably, Cao et al observed the activation of necroptosis and ferroptosis in a mouse model of chronic unpredictable mild stress-induced depression. In addition, previous studies have
demonstrated that the nuclear factor erythroid 2-related factor 2 (NRF2)/haem oxygenase 1 (HO-1) signalling pathway and superoxide dismutase regulate ROS levels in the body, which is important for OS and inflammatory damage and is closely related to depression.\textsuperscript{27, 28} NRF2 is an important nuclear factor that regulates ferroptosis and has a vital role in the antioxidant, iron metabolism and lipid peroxidation pathways.\textsuperscript{29} Wu et al reported that sulforaphane, an NRF2 activator, has an antidepressant effect in mice.\textsuperscript{30} This suggests that targeting key proteins involved in ferroptosis may be a promising strategy for the treatment and prevention of MDD.

In the present review, we aim to highlight the precise molecular mechanisms of ferroptosis, the regulatory network of ferroptosis in depression and the potential of targeted therapies for treating depression. We also aim to summarise the current research hotspots and explore breakthroughs in drug treatment for depression. Finally, we discuss the focus and urgent issues related to ferroptosis in depression.

REGULATION OF THE FERROPTOSIS PATHWAY

Ferroptosis is an iron-dependent regulatory cell death pathway characterised by excessive oxidation of polyunsaturated fatty acids (PUFAs) and the accumulation of excess iron ions, which is associated with OS. Diseases of different organs, including traumatic brain injury, stroke, and neurodegenerative disorders, have been reported to be closely related to ferroptosis (figure 1B). Previous studies have confirmed that key proteins involved in ferroptosis are also involved in the development of depression, along with OS.\textsuperscript{31} During the conversion of the PUFAs of phospholipids (PLs) into lipid peroxides, OS may stimulate neurons to produce active oxygen radicals and induce ferroptosis. Ferroptosis is a highly regulated process involving multiple metabolic changes (eg, iron and ROS metabolism) and complex signalling pathways that require several organelles. The detailed mechanisms of ferroptosis are summarised as follows.

Abnormal iron metabolism in the brain

Iron is a vital trace element that has a role in several biological processes, including inflammatory responses, OS, oxygen transport and cell metabolism.\textsuperscript{32, 33} In the brain, iron is involved in myelination, neurotransmitter synthesis and antioxidant function; however, inflammation and OS can disrupt the function of molecules involved in iron metabolism, leading to iron imbalance.

Figure 2A summarises the regulatory mechanisms of iron iron metabolism in cells. Iron ions (Fe\textsuperscript{3+}) enter the cytoplasm via transferrin channels by binding to transferrin. Inside the cell, Fe\textsuperscript{3+} is converted to ferrous ions (Fe\textsuperscript{2+}) by metalloreductases and participates in various physiological and biochemical processes, including ferroptosis. When iron storage becomes overloaded, excess Fe\textsuperscript{2+} is transported to the labile iron pool (LIP) via divalent metal transporter 1.\textsuperscript{34} Bidirectional regulation of iron metabolism is facilitated by cellular proteins. Conversely, Fe\textsuperscript{3+} enters cells through the transferrin (TF)/transferrin receptor 1 (TFR-1) transport system, and upregulation of iron-related proteins can also cause intracellular iron overload. The nuclear receptor coactivator 4 (NCOA4) protein can release free iron from ferritin via ferritinophagy, and NRF2 gene-regulated HO-1 catalyses the degradation of haem to produce Fe\textsuperscript{3+}. Finally, excess iron leads to excessive ROS production via the Fenton reaction.\textsuperscript{35} In contrast, heat shock protein family B (small) member 1 expression can inhibit the expression of TFR-1, reduce iron intake and control iron pool capacity. Free iron ions can be exported from cells by ferroportin and prominin2;\textsuperscript{36} however, free iron can cause the Fenton reaction, generating ROS, including superoxide, hydrogen peroxide and hydroxyl radicals. Accumulated ROS can cause widespread damage, ultimately leading to the loss of cell function and cell death. Recent studies have shown that iron absorption, utilisation, recovery and storage are finely regulated by a series of iron transport-related proteins such as TFR1, ferritin light chain, ferritin heavy chain 1 (FTH1), NCOA4, ferroportin and divalent metal transporter 1.\textsuperscript{37, 38} Additionally, Daar et al reported that deferasirox provided a sustained reduction in LIP levels in heavily iron-overloaded patients, further reducing unregulated tissue iron loading and preventing end-organ damage.\textsuperscript{39} Increased iron uptake and reduced iron storage may lead to an iron overload during ferroptosis.

Disturbances in ROS metabolism

Numerous studies have confirmed that lipid peroxidation is the driver of ferroptotic cell death.\textsuperscript{40} High levels of ROS lead to the oxidation of cellular biomolecules, particularly biomembrane lipids, causing lipid peroxidation.\textsuperscript{41} Figure 2B summarises the regulatory mechanisms of ROS metabolism in cells. Acyl-CoA synthetase long-chain family member 4 (ACSL4), a key regulator of fatty acid metabolism that facilitates the acylation of arachidonic acid, and lysophosphatidylcholine acyltransferase 3 (LPCAT3), an essential enzyme responsible for the reaction of lysophospholipids within cell membranes, has emerged as crucial components of ferroptosis induced by RSL3 and erasin. Lipoxygenases (LOXs) primarily serve as catalysts for the synthesis of lipid hydroperoxides, generating double-oxygenated and triple-oxygenated (15-hydroperoxy)-diacylated phosphatidylethanolamine (PE) species, which are indicative of ferroptosis. Tocopherols and tocopherols can suppress LOX activity, thereby exerting a preventive effect against ferroptosis. In addition, P53 may reduce ROS production by down-regulating cyclo-oxygenase-2, nitric oxide synthase 2 and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4.\textsuperscript{42} Finally, voltage-dependent anion channels (VDACs) regulate mitochondrial ROS production.\textsuperscript{43} Cell membranes contain large amounts of PUFAs, which are primary targets for ROS attacks. PUFAs can be involved in the subsequent oxidation process as high-energy compounds, generating many lipid peroxidation
intermediates and gradually accumulating in the cell membrane through the transport of LPCAT3. This causes a change in the cell membrane structure by altering the lipid composition, thereby inducing ferroptotic cell death. Furthermore, ROS accumulation within the cellular membrane requires the involvement of iron ions. The primary mechanism driving ferroptosis involves the catalytic activity of divalent iron or ester oxygenase, leading to heightened expression of unsaturated fatty acids on the cell membrane, ultimately causing lipid peroxidation and ensuing cellular demise. Iron ions and ROS form cross-talk and mediate ferroptosis (figure 2C,D).
Ferroptosis regulation defence systems. This schematic chart illustrates the main control regulatory systems for ferroptosis, which include the xCT-GSH-GPX4, NAD(P)H/FSP1/CoQ10 and GCH1/BH4 pathways. The canonical axis for ferroptosis control involves the uptake of cystine via the cystine-glutamate antiporter, reducing cystine to cysteine through GSH. GSH is a crucial substrate of GPX4, thus preventing ferroptosis. The FSP1/CoQ10 system in ferroptosis has been identified in two independent genetic screens that fully protect against ferroptosis induced by pharmacological inhibition or genetic deletion of GPX4. Unlike GSH/GPX4, FSP1 prevents lipid peroxidation and associated ferroptosis via the reduction of ubiquinol/α-tocopherol on the level of lipid radicals. Researchers have recently identified a new pathway for regulating ferroptosis, which involves the GCH1/BH4/DHFR axis. BH4 is an effective free radical antioxidant that can be reduced by DHFR and inhibit lipid peroxidation. BH4 also has the potential to stimulate the production of CoQ10. BH4, tetrahydrobiopterin; CoQ10, coenzyme Q10; DHFR, dihydrofolate reductase; FSP1, ferroptosis suppressor protein 1; GCH1, GTP cyclohydrolase 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSR, glutathione-disulfide reductase; IPP, intracisternal a particle-promoted polypeptide; MTX, methotrexate; NADPH, nicotinamide adenine dinucleotide phosphate; xCT, cystine/glutamate antiporter.

**Figure 3** Ferroptosis regulation defence systems. This schematic chart illustrates the main control regulatory systems for ferroptosis, which include the xCT-GSH-GPX4, NAD(P)H/FSP1/CoQ10 and GCH1/BH4 pathways. The canonical axis for ferroptosis control involves the uptake of cystine via the cystine-glutamate antiporter, reducing cystine to cysteine through GSH. GSH is a crucial substrate of GPX4, thus preventing ferroptosis. The FSP1/CoQ10 system in ferroptosis has been identified in two independent genetic screens that fully protect against ferroptosis induced by pharmacological inhibition or genetic deletion of GPX4. Unlike GSH/GPX4, FSP1 prevents lipid peroxidation and associated ferroptosis via the reduction of ubiquinol/α-tocopherol on the level of lipid radicals. Researchers have recently identified a new pathway for regulating ferroptosis, which involves the GCH1/BH4/DHFR axis. BH4 is an effective free radical antioxidant that can be reduced by DHFR and inhibit lipid peroxidation. BH4 also has the potential to stimulate the production of CoQ10. BH4, tetrahydrobiopterin; CoQ10, coenzyme Q10; DHFR, dihydrofolate reductase; FSP1, ferroptosis suppressor protein 1; GCH1, GTP cyclohydrolase 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSR, glutathione-disulfide reductase; IPP, intracisternal a particle-promoted polypeptide; MTX, methotrexate; NADPH, nicotinamide adenine dinucleotide phosphate; xCT, cystine/glutamate antiporter.

**xCT-GSH-GPX4 regulatory pathway**

The system xCT, a heterodimer transporter composed of solute carriers 7A11 and 3A2 proteins, was first discovered by Bannai et al. This transporter is responsible for exchanging intracellular glutamate with extracellular cysteine across the cell membrane and is an essential substrate for GSH synthesis. Inhibiting the xCT system consumes intracellular GSH, ultimately leading to cellular ferroptosis via ROS upregulation. Notably, the xCT-GSH-GPX4 system is a crucial antioxidant system. GPX4 is a selenocysteine-containing protein and peroxidase of GSH that catalyses the reduction of lipid peroxides, leading to the transition of GSH to glutathione.
disulfide.\textsuperscript{49, 50} GPX4 has a critical role in inhibiting ferroptosis by reducing lipid peroxide toxicity and maintaining membrane lipid bilayer homeostasis. Therefore, targeting the GPX4 degradation pathway may be crucial for inhibiting ferroptosis in neurons and alleviating depressive symptoms.

**NAD(P)H/FSP1/CoQ10 regulatory pathway**

Bersuker et al found that FSP1 is a key component of the non-mitochondrial CoQ10 antioxidant system, which works in parallel with the canonical GSH-based GPX4 pathway to inhibit ferroptosis.\textsuperscript{51} CoQ10 was first purified from bovine heart in 1956 and functions as an electron carrier in the electron transport chain. NAD(P)H serves as the electron source in this system, whereas FSP1 reduces the oxidised form of CoQ10, which acts as a lipophilic free radical-scavenging antioxidant in the plasma membrane.\textsuperscript{51} Mechanistically, the ubiquinone outside the mitochondria is reduced from CoQ10 by FSP1, which can either directly capture lipid-free radicals or act as an antioxidant indirectly through the recovery of alpha-tocopherol; however, the detailed molecular mechanism of FSP1 action requires further investigation.

**GCH1-BH4 regulatory pathway**

GCH1 is another important regulator of ferroptosis and mediates the rate-limiting reactions in the BH4, a cofactor of aromatic amino acid hydroxylase and other enzymes, biosynthesis pathway. As shown in figure 3, BH4 is an antioxidant capable of trapping lipid peroxidation-free radicals. Importantly, GCH1 can selectively prevent the degradation of dihydroubiquione (CoQH2) and PL with two PUFA tails, and has a role in ferroptosis defence. Thus, the GCH1-BH4-PL axis may be a potential target for treating related diseases in clinical practice.

**THE ROLE OF FERROPTOSIS IN THE PATHOLOGICAL MECHANISM OF DEPRESSION**

Depressive symptoms are associated with hippocampal neuronal dysfunction and death.\textsuperscript{52} Although previous studies have revealed that inhibition of ferroptosis has antidepressant functions, the regulatory mechanism of ferroptosis in MDD needs to be further understood. Since the target genes regulated by ferroptosis are involved in a variety of pathological processes, their roles in depression may also be multifaceted. Therefore, we summarised the potential mechanisms of ferroptosis and depression from the following aspects (figure 4).

**The role of abnormal iron metabolism in depression**

Iron in brain tissue mainly comes from serum iron transported through the cerebral microvasculature, and Fe\textsuperscript{3+} entering the brain tissue can be absorbed and used by neurons and glial cells.\textsuperscript{53} Epidemiological and animal studies have indicated that many metal ions can cause emotional regulation disorders and insomnia.\textsuperscript{54} For example, studies have shown that metal ions in serum increase the risk of depression and insomnia.\textsuperscript{55} Iron in neurons and glial cells should be maintained at a certain level; excessive accumulation of iron leads to an increase in the LIP and ROS, which can cause neuronal damage.\textsuperscript{56} The aetiology of depression is complex and determined by both genetic and environmental factors. A recent study demonstrated ferroptosis in the hippocampus of an MDD mouse model and indicated that the incidence of depression may be associated with ferroptosis-related pathways.\textsuperscript{57} Free Fe\textsuperscript{2+} plays a significant role in catalysing the formation of oxygen free radicals in cells and initiating the chain reaction of lipid peroxidation by abstracting hydrogen from PUFA. The occurrence and development of depression are closely related to changes in the iron ion levels in the human body. Iron ions have a significant effect on the synthetic pathways of neurotransmitters, conduction of nervous impulses and functional regulation of receptors, which have crucial implications for memory, behaviour and cognitive function.\textsuperscript{58}
**Figure 4** The potential role of ferroptosis in depression. The molecular mechanism of ferroptosis is involved in the progression of depression. Chronic stress can induce iron overload and the production of ROS in neurons. ACSL4, acyl-CoA synthetase long-chain family member 4; FPN1, ferroportin 1; GPX4, glutathione peroxidase 4; GSH, glutathione; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; TFR1, transferrin receptor 1.

NRF2, an important antioxidant, expressed at low levels in the cortex and hippocampus, is a significant downstream target of Sirt1 and serves a crucial role in improving OS resistance. Previous studies have indicated that NRF2 knockout mice exhibited depression-like behaviour, and models of chronic unpredictable mild stress demonstrated decreased NRF2 expression in the rat hippocampus. Accumulating evidence suggests a close link between the NRF2/HO-1 pathway and MDD, suggesting its crucial role in the treatment of depression. Recent research has shown that polydatin inhibits chronic stress-induced depression-like behaviours by upregulating NRF2 expression. The therapeutic effects of several antidepressants have been found to be strongly associated with NRF2.

Another study showed significant changes in the expression of GPX4, FTH1, ACSL4 and total iron in the hippocampi of mice with depressive-like behaviours. Xiaoyaosan and fluoxetine improve behavioural changes by regulating PE binding protein 1 (PEBP1)-GPX4-mediated ferroptosis. Furthermore, PEBP1 increases the production of hydroperoxy-PE by forming a complex with 15 lipoygenase (LO) 1 and 15LO2, which blocks GPX4 synthesis and leads to ferroptosis. Additionally, reduced levels of zinc, CoQ10, vitamin C/E and GSH have been associated with low total antioxidant capacity in patients with MDD.

**TARGETING FERROPTOSIS TO TREAT DEPRESSION**

Recently, several compounds that inhibit ferroptosis have been successfully approved for clinical use and have advanced to the late stages of clinical trials (online supplemental table 1). Currently, common inhibitors of ferroptosis target two key points in the ferroptosis pathway: iron overload and lipid peroxide accumulation. They primarily inhibit ferroptosis by reducing free Fe^{2+}, eliminating oxygen radicals and inhibiting lipid peroxidation. We further summarise the features of drugs that inhibit ferroptosis, either in clinical use or with strong translational potential, including iron chelators, radical-trapping antioxidants, natural compounds and other ferroptosis inhibitors (figure 5 and table 1).

**Iron chelators**

Iron chelators prevent the formation of highly reactive hydroxyl radicals by removing excess iron. To date, two
Figure 5  The structure of small molecule ferroptosis inhibitors. These inhibitors come in various forms, such as (A) iron chelators that hinder intracellular Fe\(^{2+}\), (B) radical-trapping antioxidants that impede the role of reactive oxygen species (ROS) and (C) natural compounds that block the acyl-CoA synthetase long-chain family member 4 (ACSL4) protein. THN, tetrahydronaphthyridinols.

types of iron chelators have been reported. The first type, such as deferiprone, separates iron atoms from the cytoplasm, thereby blocking the process of ferroptosis. Preclinical studies have shown that iron chelation therapy can prevent ferroptosis in patients with intracerebral haemorrhage.70 More recently, deferiprone has been used to prevent iron pathological processes in neurodegenerative diseases such as Parkinson’s disease and Friedreich’s

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS no.</th>
<th>Target</th>
<th>Mechanism</th>
<th>Ref. PMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferiprone</td>
<td>30652-11-0</td>
<td>Iron</td>
<td>Reduces intracellular iron</td>
<td>22632970</td>
</tr>
<tr>
<td>Deferoxamine</td>
<td>138-14-7</td>
<td>Iron</td>
<td>Reduces intracellular iron</td>
<td>22632970</td>
</tr>
<tr>
<td>Curcumin</td>
<td>458-37-7</td>
<td>Iron; Keap1</td>
<td>Reduces iron accumulation and activates NRF2 signalling pathway</td>
<td>30736288</td>
</tr>
<tr>
<td>Ferrostatin-1</td>
<td>347174-05-4</td>
<td>Lipid ROS</td>
<td>Inhibits lipid peroxidation</td>
<td>31034781</td>
</tr>
<tr>
<td>Liproxstatin-1</td>
<td>950455-15-9</td>
<td>Lipid ROS</td>
<td>Inhibits lipid peroxidation</td>
<td>28386601</td>
</tr>
<tr>
<td>THN</td>
<td>18512-30-6</td>
<td>Lipid ROS</td>
<td>Reduces intracellular ROS</td>
<td>28386601</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>122320-73-4</td>
<td>ACSL4</td>
<td>Suppresses the ACSL4 protein and reduces intracellular ROS</td>
<td>35038927</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>111025-46-8</td>
<td>ACSL4</td>
<td>Suppresses the ACSL4 protein and reduces intracellular ROS</td>
<td>35038927</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>97322-87-7</td>
<td>ACSL4</td>
<td>Suppresses the ACSL4 protein and reduces intracellular ROS</td>
<td>27842070</td>
</tr>
</tbody>
</table>

ACSL4, acyl-CoA synthetase long chain family member 4; NRF2, nuclear factor erythroid 2-related factor 2; Ref, reference; ROS, reactive oxygen species; THN, tetrahydronaphthyridinols.
Ferroptosis inhibitors

ACSL4 has a key role in the synthesis of long-chain PUFAs-CoA by esterifying free fatty acids. Several studies have reported that rosiglitazone, pioglitazone and troglitazone can specifically inhibit ACSL4 but not other ACSL subtypes. Although troglitazone has a low inhibitory effect on ACSL4, it may have inherent antioxidant activity because of its 6-chromenoalkanol structure, which is the most protective thiazolidinedione.

CONCLUSIONS

Recent literature suggests that OS and impaired antioxidant defence systems, induced by ROS production, have crucial roles in the pathogenesis of MDD. OS can induce or exacerbate a range of pathological processes, including ferroptosis. In this regard, we summarised the interaction network of iron ions and ROS, and several regulatory pathways (ie, xCT-GSH-GPX4, NAD(P)H/FSP1/CoQ10 and GCH1/BH4) involved in ferroptosis. Ferroptosis may be a key mechanism in the pathogenesis of depression; its inhibition could prevent damage to neurons and astrocytes and improve depressive symptoms. Currently, common inhibitors of ferroptosis mainly target two key aspects of the ferroptotic pathway: iron overload and lipid peroxide accumulation. Although various ferroptosis inhibitors have been discovered, the targets and potential applications of most of these compounds remain unknown. Therefore, it is necessary to further elucidate the mechanisms of these compounds and explore the possibility of drug combinations that will have a profound impact on their clinical applications in the future.

Contributors
Song Q, Shan Q, GH and GY identified the topic, planned the review. HZ, ZL and RY did the reference search. LW undertook the literature review, contributed to the writing and prepared bibliography for this paper formatting in line with General Psychiatry referencing requirements.

Funding
This project was supported by the President Foundation of Nanfang Hospital, Southern Medical University (2022A018) and the China Postdoctoral Research Foundation (2021M7016).

Competing interests
None declared.

Patient consent for publication
Not applicable.

Ethics approval
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES


8 Su YA, SI T. Progress and challenges in the research of the mechanisms of anhedonia in major depressive disorder. *Gen Psychiatr* 2022;35:e100774.


Luyao Wang has a 5-year undergraduate degree in clinical medicine at Southern Medical University. Luyao Wang has been actively participating in public welfare social practices in the 3 years since entering university to do her best to help people who need help.