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ROZPRAWA DOKTORSKA

Ocena wybranych parametrów biochemicznych u chorych na depresję jako potencjalnych biomarkerów

Autor: lek. Aleksander Nobis

Promotor: prof. dr hab. Napoleon Waszkiewicz

Klinika Psychiatrii

Kierownik jednostki: prof. dr hab. Napoleon Waszkiewicz

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DOCTORAL THESIS

Evaluation of selected biochemical parameters in patients with depression as potential biomarkers

Author: lek. Aleksander Nobis

First supervisor: prof. dr hab. Napoleon Waszkiewicz

Department of Psychiatry

Head of department: prof. dr hab. Napoleon Waszkiewicz

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Spis treści

1. Wykaz stosowanych skrótów

3-HAA	*3-hydroxyanthranilic acid*	kwas 3-hydroksyantranilowy
3-HK	*3-hydroxykynurenine*	3-hydroksykinurenina
3-NT	*3-nitrotyrosine*	3-nitrotyrozyna
4-HNE	*4-hydroxy-2-nonenal*	4-hydroksy-2-nonenal
5-HIAA	*5-hydroxyindoleacetic acid*	kwas 5-hydroksyindolooctowy
5-HT	*serotonin*	serotonina
8-OHdG	*8-hydroxy-2-deoxiguanosine*	8-hydroksy-2-deoksyguanozyna
8-oxo-Guo	*8-oxo-7,8-dihydroguanosine*	8-okso-7,8-dihydroguanozyna
ACE	*angiotensin-converting enzyme*	enzym konwertujący angiotensynę
ACTH	*adrenocorticotropic hormone*	hormon adrenokortykotropowy
AD	*Alzheimer's disease*	choroba Alzheimera
ADH	*antidiuretic hormone*	hormon antydiuretyczny
AGE	*advanced glycation end-products*	zaawansowane końcowe produkty glikacji
ALT	*alanine aminotransferase*	aminotransferaza alaninowa
AOPP	*advanced oxidation protein products*	zaawansowane produkty utleniania białek
APP	*acute phase proteins*	białka ostrej fazy
AST	*aspartate aminotransferase*	aminotransferaza asparaginianowa
ATP	*adenosine triphosphate*	adenozynotrifosforan
BDI	*Beck depression inventory*	skala depresji Becka
BDNF	*brain-derived neurotrophic factor*	czynnik neurotroficzny pochodzenia mózgowego
BMI	*body mass index*	wskaźnik masy ciała
BPD	*bipolar disorder*	zaburzenie afektywne dwubiegunowe
Ca^{2+}	*calcium ions*	jony wapnia
cAMP	*cyclic adenosine monophosphate*	cykliczny monofosforan adenozyny
CAT	*catalase*	katalaza
CD4	*cluster of differentiation 4*	antygen różnicowania komórkowego 4
CD8	*cluster of differentiation 8*	antygen różnicowania komórkowego 8

CIRS	*compensatory immune-regulatory reflex system*	kompensacyjny system immunoregulacji
COMT	*catechol-O-methyltransferase*	katecholo-O-metylotransferaza
CoQ	*coenzyme Q*	koenzym Q
CRE	*cyclic adenosine monophosphate response elements*	czynnik odpowiedzi cyklicznego monofosforanu adenozyny
CREB	*cyclic adenosine monophosphate response element binding protein*	białko wiążące czynnik odpowiedzi cyklicznego monofosforanu adenozyny
CRF	*corticotropin-releasing factor*	czynnik uwalniający kortykotropinę
CRH	*corticotropin-releasing hormone*	hormon uwalniający kortykotropinę
CRP	*C-reactive protein*	białko C-reaktywne
CSF	*cerebrospinal fluid*	płyn mózgowo-rdzeniowy
CVD	*cardiovascular disease*	choroba układu krążenia
DA	*dopamine*	dopamina
DALYs	*disability-adjusted life years*	lata życia skorygowane o niepełnosprawność
DHEA	*dehydroepiandrosterone*	dehydroepiandrosteron
DNA	*deoxyribonucleic acid*	kwas dezoksyrybonukleinowy
DSM-5	*Diagnostic and Statistical Manual – 5th Edition*	Podręcznik Diagnostyczny i Statystyczny – wydanie 5
DST	*dexamethasone suppression test*	test hamowania deksametazonem
ECT	*electroconvulsive therapy*	terapia elektrowstrząsowa
EEG	*electroencephalography*	elektroencefalografia
EPA	*eicosapentaenoic acid*	kwas eikozapentaenowy
ESR	*erythrocyte sedimentation rate*	odczyn Biernackiego
FGF-2	*fibroblast growth factors 2*	czynniki wzrostu fibroblastów 2
GABA	*gamma-aminobutyric acid*	kwas gamma-aminomasłowy
GDNF	*glial cell line derived neurotrophic factor*	czynnik neurotroficzny pochodzenia glejowego
GH	*growth hormone*	hormon wzrostu
GPx	*glutathione peroxidase*	peroksydaza glutationowa
GSH	*reduced glutathione*	zredukowany glutation
GSK-3	*glycogen synthase kinase 3*	kinaza syntazy glikogenu 3
HAM-A	*Hamilton anxiety rating scale*	skala oceny lęku Hamiltona

HAM-D	*Hamilton depression rating scale*	skala oceny depresji Hamiltona
HDRS	*Hamilton depression rating scale*	skala oceny depresji Hamiltona
HDL	*high-density lipoprotein*	lipoproteina o wysokiej gęstości
HPA	*hypothalamus–pituitary–adrenal*	podwzgórze-przysadka-nadnercza
hsCRP	*high sensitivity C-reactive protein*	białko C-reaktywne o wysokiej czułości
HVA	*homo-vanillic acid*	kwas homowaniliowy
ICD-11	*International Classification of Diseases, 11th edition*	Międzynarodowa Klasyfikacja Chorób, wydanie 11
IDO	*indoleamine 2,3-dioxygenase*	2,3-dioksygenaza indoloaminy
IFN-γ	*interferone γ*	interferon γ
IGF-1	*insulin-like growth factor-1*	insulinopodobny czynnik wzrostu 1
IGFBP1	*insulin-like growth factor-binding protein 1*	białko wiążące insulinopodobny czynnik wzrostu 1
IGFBP2	*insulin-like growth factor-binding protein 2*	białko wiążące insulinopodobny czynnik wzrostu 2
IgG	*immunoglobulin G*	immunoglobulina G
IgM	*immunoglobulin M*	immunoglobulina M
IL-1	*interleukin 1*	interleukina 1
IL-1β	*interleukin 1β*	interleukina 1β
IL-1RA	*interleukin 1 receptor antagonist*	antagonista receptora interleukiny 1
IL-2	*interleukin 2*	interleukina 2
IL-2R	*interleukin 2 receptor*	receptor interleukiny 2
IL-3	*interleukin 3*	interleukina 3
IL-4	*interleukin 4*	interleukina 4
IL-6	*interleukin 6*	interleukina 6
IL-6R	*interleukin 6 receptor*	receptor interleukiny 6
IL-8	*interleukin 8*	interleukina 8
IL-10	*interleukin 10*	interleukina 10
IL-12	*interleukin 12*	interleukina 12
IL-13	*interleukin 13*	interleukina 13
IL-18	*interleukin 18*	interleukina 18
iNOS	*cytokine-inducible nitric oxide synthase*	syntaza tlenku azotu indukowana cytokinami

IRS	*immune-inflammatory response system*	układ odpowiedzi odpornościowo-zapalnej
JAK-STAT	*Janus kinases-signal transducer and activator of transcription*	przetwornik sygnału i aktywator transkrypcji kinaz janusowych
KN	*kynurenine*	kinurenina
KYN	*kynurenine*	kinurenina
KYNA	*kynurenic acid*	kwas kinurenowy
LDL	*low-density lipoprotein*	lipoproteina o niskiej gęstości
lncRNA	*long non-coding RNA*	długi niekodujący RNA
LPS	*lipopolysaccharide*	lipopolisacharyd
LTP	*long-term potentiation*	długotrwałe wzmocnienie synaptyczne
LTT	*lymphocyte transformation test*	test transformacji limfocytów
MADRS	*Montgomery-Asberg depression rating scale*	skala oceny depresji Montgomery-Asberg
MAO-B	*monoamine oxidase B*	oksydaza monoaminowa B
MAP	*microglial activation and proliferation*	aktywacja i proliferacja mikrogleju
MAPK/ERK	*mitogen-activated protein kinase/extracellular signal-regulated kinases*	kinazy białkowe aktywowane mitogenem/ zewnątrzkomórkowe kinazy regulowane sygnałem
MCP1/CCL2	*monocyte chemoattractant protein 1/chemokine ligand 2*	białko chemotaktyczne monocytów-1/ligand chemokinowy 2
MDA	*malonylodialdehyde*	malonylodialdehyd
MDD	*major depressive disorder*	depresja
MHPG	*3-methoxy-4-hydroxyphenylglycol*	glikol 3-metoksy-4-hydroksyfenylowy
MIF	*macrophage migration inhibitory factor*	czynnik hamujący migrację makrofagów
MPO	*myeloperoxidase*	mieloperoksydaza
NA	*noradrenaline*	noradrenalina
NAA	*N-acetylaspartate*	N-acetyloasparaginian
N-ACC	*N-acetylo-cysteine*	N-acetylo-cysteina
NFKN	*N-formylkynurenine*	N-formylokinurenina
NGF	*nerve growth factor*	czynnik wzrostu nerwów
NK	*natural killer*	naturalny zabójca
NKCA	*natural killer cell activity*	aktywność komórek NK
NMD	*non-melancholic depression*	depresja niemelancholiczna

NMDAR	*N-methyl-D-aspartate receptor*	receptor N-metylo-D-asparaginianu
nNOS	*neuronal nitric oxide synthase*	neuronalna syntaza tlenku azotu
NOS	*nitric oxide synthase*	syntaza tlenku azotu
O&NS	*oxidative and nitrosative stress*	stres oksydacyjny i nitrozowy
OPN	*osteopontin*	osteopontyna
CNS	*central nervous system*	ośrodkowy układ nerwowy
oxLDL	*oxidized low-density lipoprotein*	utlenione lipoproteiny o małej gęstości
PET	*positron emission tomography*	pozytonowa tomografia emisyjna
PUFA	*polyunsaturated fatty acid*	wielonienasycony kwas tłuszczowy
QA	*quinolinic acid*	kwas chinolinowy
RA	*rheumatoid arthritis*	reumatoidalne zapalenie stawów
RANK	*receptor activator of nuclear factor κ-B*	aktywator receptora czynnika jądrowego κ-B
RANKL	*receptor activator of nuclear factor κ-B ligand*	aktywator receptora liganda czynnika jądrowego κ-B
RDoC	*Research Domain Criteria Initiative*	Inicjatywa kryteriów domeny badawczej
RNA	*ribonucleic acid*	kwas rybonukleinowy
RNS	*reactive nitrogen species*	reaktywne formy azotu
ROC AUC	*area under the receiver operating characteristic curve*	obszar pod krzywą charakterystyki pracy odbiornika
ROS	*reactive oxygen species*	Reaktywne formy tlenu
sIL-2R	*soluble interleukin 2 receptor*	rozpuszczalny receptor interleukiny 2
sIL-6R	*soluble interleukin 6 receptor*	rozpuszczalny receptor interleukiny 6
SNRI	*selective serotonin-norepinephrine reuptake inhibitor*	selektywny inhibitor wychwytu zwrotnego serotoniny i noradrenaliny
SOD	*superoxide dismutase*	dysmutaza ponadtlenkowa
SSRI	*selective serotonin reuptake inhibitor*	selektywny inhibitor wychwytu zwrotnego serotoniny

sTNF-R1	*soluble tumor necrosis factor receptor 1*	rozpuszczalny receptor czynnika martwicy nowotworu 1
sTNF-R2	*soluble tumor necrosis factor receptor 2*	rozpuszczalny receptor czynnika martwicy nowotworu 2
TAC	*total antioxidant capacity*	całkowita zdolność antyoksydacyjna
TBARS	*thiobarbituric acid reactive substances*	substancje reagujące z kwasem tiobarbiturowym
TC	*total cholesterol*	cholesterol całkowity
TCA	*tricyclic antidepressants*	trójpierścieniowe leki przeciwdepresyjne
TGA	*triglycerides*	trójglicerydy
TGF-β	*transforming growth factor β*	transformujący czynnik wzrostu β
TNF-α	*tumour necrosis factor α*	czynnik martwicy nowotworu α
TOS	*total oxidant status*	całkowity status oksydacyjny
TRD	*treatment-resistant depression*	depresja oporna na leczenie
Tregs	*regulatory T cells*	limfocyty T regulatorowe
TRP	*tryptophan*	tryptofan
TRY	*tryptophan*	tryptofan
TRYCAT	*tryptophan catabolites*	katabolity tryptofanu
TSH	*thyroid-stimulating hormone*	hormon stymulujący tarczycę
VEGF	*vascular endothelial growth factor*	czynnik wzrostu śródbłonka naczyń
WHO	*World Health Organization*	Światowa Organizacja Zdrowia

2. Wykaz publikacji stanowiących rozprawę doktorską

Praca przeglądowa:

1. **Aleksander Nobis**, Daniel Zalewski, Napoleon Waszkiewicz: *Peripheral Markers of Depression*. Journal of Clinical Medicine 2020. 9 (12) 3793. Doi: 10.3390/jcm9123793

IF = 4,242, MNiSW = 140

Praca oryginalna:

1. **Aleksander Nobis**, Daniel Zalewski, Eliza Samaryn, Mateusz Maciejczyk, Anna Zalewska, Napoleon Waszkiewicz: *Urine 3-Nitrotyrosine and Serum HDL as Potential Biomarkers of Depression*. Journal of Clinical Medicine 2023. 12 (1) 377. Doi: 10.3390/jcm12010377

IF = 3,9, MNiSW = 140

3. Zestawienie publikacji doktoranta

Rodzaj publikacji	Liczba	Impact factor	Punktacja MNiSW
Prace włączone do rozprawy doktorskiej	2	8,142	280
Prace, które nie zostały włączone do rozprawy doktorskiej	2	2,658	30
Razem	**4**	**10,8**	**310**

4. Wstęp

Depresja (zaburzenie depresyjne, ang. *Major Depressive Disorder*, MDD) jest jednym z najczęściej występujących zaburzeń psychicznych na świecie. Szacuje się, że dotyka ona 350 milionów osób, czyli około 5% światowej populacji[1]. Charakteryzuje się wysokim odsetkiem samobójstw oraz dużą liczbą lat życia skorygowanych niesprawnością (DALY)[2]. Depresja znacznie obniża jakość życia pacjenta, stanowiąc istotne wyzwanie dla systemów ochrony zdrowia na całym świecie. Rozpoznanie epizodu depresji, wg. Międzynarodowej Klasyfikacji Chorób, wydania 11 (ICD-11), ustala się na podstawie współistnienia szeregu objawów, które utrzymują się w sposób stały lub przez większość dni, przez okres co najmniej dwóch tygodni. Do rozpoznania konieczne jest stwierdzenie u pacjenta obniżonego nastroju (lub utraty zainteresowań i odczuwania przyjemności) oraz co najmniej pięciu spośród objawów dodatkowych (trudności z koncentracją, poczucie bezwartościowości lub nieadekwatne poczucie winy, uczucie beznadziei, nawracające myśli o śmierci lub samobójstwie, zmiany w zakresie apetytu lub snu, agitacja lub spowolnienie psychoruchowe oraz obniżony poziom energii lub wzmożona męczliwość). W przypadku wystąpienia w ciągu życia kolejnego epizodu depresji, rozpoznanie zmieniane jest na zaburzenia depresyjne nawracające[3].

Różnorodność manifestacji klinicznych MDD stanowi wyzwanie w diagnostyce różnicowej choroby, a etiopatogeneza zaburzenia jest wieloczynnikowa i złożona. W dalszym ciągu pozostaje ona nie w pełni wyjaśniona. Wskazuje się na wpływ czynników psychologicznych, społecznych i biologicznych na powstawanie depresji. Pośród czynników biologicznych mających wpływ na ujawnienie się depresji, należy wymienić predyspozycje genetyczne, zaburzenia przekaźnictwa monoaminergicznego, rozregulowanie osi stresu (podwzgórze – przysadka – nadnercza) oraz stan nierównowagi pomiędzy procesami zapalnymi i

przeciwzapalnymi. Stres oksydacyjny i nitrozowy (O&NS), ściśle powiązany z procesami zapalnymi, jest również wymieniany jako jeden z kluczowych czynników biologicznych zaangażowanych w powstawanie depresji[4]. Stres oksydacyjny to utrzymujący się stan zaburzenia równowagi pomiędzy systemami obrony antyoksydacyjnej a uszkodzeniami powodowanymi przez reaktywne formy tlenu (ROS), na korzyść tych drugich. Reaktywne formy tlenu stanowią produkt uboczny mitochondrialnego łańcucha oksydacyjnego. Do głównych ROS należą nadtlenek wodoru, rodnik hydroksylowy i anion ponadtlenkowy[5]. Należy podkreślić, że mózg jest organem szczególnie narażonym na uszkodzenia związane ze stresem oksydacyjnym ze względu na duże zużycie tlenu w przeliczeniu na jednostkę masy ciała, wysoką zawartość nienasyconych kwasów tłuszczowych oraz ograniczone działanie systemu obrony antyoksydacyjnej. Stres nitrozowy natomiast jest miarą szkodliwego wpływu wywieranego na komórki organizmu przez reaktywne formy azotu (RNS). Przykładami RNS są tlenek azotu i peroksyazotyn. W tkance mózgowej pobranej *post mortem* od pacjentów z depresją stwierdzono wysoką zawartość reaktywnych form tlenu i azotu[6]. W warunkach fizjologii ROS i RNS są neutralizowane przez organizm na kilka sposobów. Jednym z nich jest tzw. wymiatanie wolnych rodników, np. poprzez zredukowany glutation. Innym – dezaktywacja enzymatyczna, np. poprzez dysmutazę ponadtlenkową (SOD), peroksydazę glutationową (GPx) i katalazę (CAT). Stres oksydacyjny i nitrozowy, do pewnego stopnia, podlega autoregulacji w pętli ujemnego sprzężenia zwrotnego. Wzajemne oddziaływanie na siebie systemów pro- i antyoksydacyjnych w depresji zostało szczegółowo opisane przez Maesa i Carvalho[7]. W sytuacji niedostatecznego równoważenia procesów oksydacyjnych przez układy antyoksydacyjne, ROS i RNS uszkadzają makrocząsteczki komórkowe, takie jak białka, lipidy i kwas deoksyrybonukleinowy (DNA). Prowadzi to do powstawania tzw. neoepitopów, które powodują wzmożoną odpowiedź autoimmunologiczną ustroju, czym przyczyniają się do nasilenia stanu zapalnego. Obecność takich uszkodzeń została

potwierdzona u pacjentów cierpiących na depresję[8]. Istnieją dowody na to, że MDD może być również postrzegana jako choroba neurodegeneracyjna[9]. Aktywowane szlaki O&NS sprzyjają nasileniu procesu neurodegeneracji w obrębie ośrodkowego układu nerwowego (CNS). Swój udział mają tu różne mechanizmy, m.in. bezpośredni szkodliwy wpływ ROS i RNS na tkankę mózgową, zaostrzenie procesów zapalnych w obrębie CNS, jak również neurotoksyczne działanie metabolitów powstających w wyniku aktywowanego przez ROS szlaku kinureninowego. Stres oksydacyjny i neurodegeneracja są ze sobą ściśle powiązane. Stres oksydacyjny odgrywa istotna rolę w etiologii chorób neurodegeneracyjnych, takich jak choroba Alzheimera (AD), charakteryzująca się obecnością płytek amyloidu-β w tkance mózgowej. Co ciekawe, dowiedziono, że depresja, szczególnie pojawiająca się po raz pierwszy w starszym wieku, jest prodromem i czynnikiem ryzyka wystąpienia AD. Ponadto, część objawów MDD przypomina objawy występujące w AD[10]. Z tego względu przeprowadzano oznaczenia β-amyloidu u osób cierpiących na depresję, zwłaszcza u starszych pacjentów, uzyskując jednakże sprzeczne wyniki badań[11,12]. W większości badań z wykorzystaniem pozytonowej tomografii emisyjnej (PET), w korze mózgowej pacjentów w podeszłym wieku chorujących na depresję stwierdzono wyższe poziomy złogów β-amyloidu[13–15], choć odnotowano również przeciwstawne wyniki badań[16,17].

Wyzwaniem w procesie diagnostycznym i terapeutycznym w psychiatrii jest niejednokrotnie brak obiektywnych, biologicznych wykładników choroby psychicznej. Z tego powodu proces diagnostyczny w psychiatrii opiera się w głównej mierze na informacjach uzyskanych od pacjenta i jego rodziny oraz obserwacji zachowania chorego. Sprawia to, że ostateczna diagnoza, inaczej niż w wielu innych dziedzinach medycyny, jest oparta na, w pewnym stopniu subiektywnej, ocenie lekarza. Współczesne badania naukowe w dziedzinie psychiatrii, koncentrują się m.in. na poszukiwaniu biomarkerów zaburzeń

psychicznych. Obecność dobrze zdefiniowanych, zwalidowanych biomarkerów może pozwolić na obiektywizację diagnozy oraz zaproponowanie pacjentom bardziej spersonalizowanego leczenia. Rosnąca liczba dowodów naukowych wskazuje na istnienie szeregu biochemicznych markerów MDD, na podstawie których można odróżnić pacjentów chorujących na depresję od zdrowej populacji[18,19]. Niektóre z nich mogą znaleźć zastosowanie w monitorowaniu odpowiedzi na leczenie lub przewidywaniu zwiększonego ryzyka wystąpienia depresji, zanim jeszcze się ona ujawni[20]. Markery nasilenia stresu oksydacyjnego i nitrozowego mogą być interesujące w kontekście diagnozowania i leczenia depresji oraz głębszego rozumienia mechanizmów patogenetycznych odpowiedzialnych za ujawnienie się zaburzenia. Potencjalnymi źródłami biomarkerów mogą być różne płyny ustrojowe, jak krew, mocz czy ślina. Większość badań dotyczących biomarkerów MDD koncentruje się na cząsteczkach obecnych we krwi pacjentów. Na przykład metaanaliza Carvalho i in. [21] wskazuje na kilka obiecujących biomarkerów depresji – interleukinę 6 (IL-6), białko C-reaktywne (CRP), czynnik martwicy nowotworów α (TNF-α), malonodialdehyd (MDA), F2-izoprostany, glutaminian, cholesterol całkowity (TC), czynnik neurotroficzny pochodzenia mózgowego (BDNF), czynnik wzrostu fibroblastów-2 (FGF-2) i insulinopodobny czynnik wzrostu 1 (IGF-1). Biomarkery oznaczane w moczu stanowią interesującą alternatywę dla biomarkerów z krwi, ze względu na prosty i nieinwazyjny sposób pobierania materiału biologicznego oraz fakt, że stężenie biomarkerów w moczu może przynajmniej częściowo odzwierciedlać ich stężenie we krwi.

5. Cel rozprawy doktorskiej

Celem pracy było poszukiwanie potencjalnych obwodowych biomarkerów depresji.

6. Omówienie prac składających się na pracę doktorską

6.1 Praca przeglądowa pt. „Peripheral markers of depression"

Celem pracy był szeroki przegląd dostępnej literatury naukowej dotyczącej biomarkerów depresji, z zamiarem uwzględnienia jak najszerszego spektrum różnych biomarkerów opisywanych w tym zaburzeniu.

W pracy zostały opisane markery stanu zapalnego, takie jak CRP, IL-6, TNF-α i rozpuszczalny receptor dla interleukiny 2 (sIL2R) oraz markery stresu oksydacyjnego i nitrozowego, w tym markery peroksydacji lipidów. Uwzględniono też markery świadczące o rozregulowaniu osi stresu, m.in. zwiększony poziom kortyzolu, a także markery należące do metabolitów szlaku kinureninowego. Zwrócono uwagę na zaburzenia stężeń czynników wzrostu, m.in. obniżone stężenie BDNF i podwyższone stężenia FGF-2 i IGF-1, a także na zwiększone stężenie glutaminianu i obniżone stężenie TC. Ponadto, w pracy zawarto szeroki przegląd innych potencjalnych biomarkerów, wraz z opisem niektórych kluczowych mechanizmów patofizjologicznych.

Na dzień 17.08.2023 praca uzyskała 116 cytowań według bazy PubMed.

Szczegółowe informacje dotyczące celu pracy, metod oraz wniosków zostały zaprezentowane w pracy przeglądowej wchodzącej w skład rozprawy doktorskiej:

Aleksander Nobis, Daniel Zalewski, Napoleon Waszkiewicz: *Peripheral Markers of Depression*. Journal of Clinical Medicine 2020. 9 (12) 3793. Doi: 10.3390/jcm9123793

6.2 Praca oryginalna pt. „Urine 3-Nitrotyrosine and Serum HDL as Potential Biomarkers of Depression"

Szczegółowe informacje dotyczące celu pracy, materiałów i metod, wyników oraz wniosków zostały zaprezentowane w pracy oryginalnej wchodzącej w skład rozprawy doktorskiej:

6.2.1 Cel pracy

Celem pracy była ocena markerów nasilenia stresu oksydacyjnego i nitrozowego oraz β-amyloidu w moczu oraz wybranych parametrów biochemicznych w surowicy chorych na depresję w porównaniu do osób zdrowych w grupie kontrolnej.

6.2.2 Materiał i metody

6.2.2.1 Grupa badana i kontrolna

Uczestników badania rekrutowano spośród pacjentów hospitalizowanych z rozpoznaniem MDD w okresie od grudnia 2021 r. do lipca 2022 r. w Samodzielnym Publicznym Psychiatrycznym Zakładzie Opieki Zdrowotnej im. Dr. Stanisława Deresza w Choroszczy. Do badania włączono łącznie 29 pacjentów (11 mężczyzn, 18 kobiet) w wieku od 18 do 65 lat. Średnia wieku wynosiła 43,3 lat. Wszyscy pacjenci byli Polakami, należeli do rasy kaukaskiej. W badanej grupie było 4 (13,8%) pacjentów z pierwszym epizodem depresji i 25

(86,2%) z rozpoznaniem zaburzeń depresyjnych nawracających . Z udziału w badaniu wykluczono kobiety w ciąży i karmiące piersią oraz osoby z otyłością, cukrzycą, chorobami zapalnymi, autoimmunologicznymi i endokrynologicznymi. Wszyscy pacjenci przed rekrutacją do badania otrzymywali już leki z grupy selektywnych inhibitorów wychwytu zwrotnego serotoniny (SSRI) lub selektywnych inhibitorów wychwytu zwrotnego serotoniny i noradrenaliny (SNRI) lub wortioksetynę. Grupę kontrolną rekrutowano spośród zdrowych ochotników dobranych pod względem płci i wieku tak, aby odpowiadały osobom w grupie badanej. Grupę kontrolną stanowiło 30 osób (10 mężczyzn, 20 kobiet) w średnim wieku 41,8 lat. Badanie zostało przeprowadzone zgodnie z Wytycznymi Dobrej Praktyki Klinicznej oraz Deklaracją Helsińską. Wszyscy uczestnicy badania podpisali formularze świadomej zgody.

6.2.2.2 Protokół badania

Rozpoznanie depresji (tj. epizodu depresyjnego lub zaburzenia depresyjnego nawracającego) było stawiane w oparciu o kryteria ICD-11 i potwierdzone przez doświadczonego psychiatrę. W celu wykluczenia innych potencjalnych jednostek psychiatrycznych, stosowano ustrukturyzowany kwestionariusz wywiadu (MINI)[22]. Tak zakwalifikowani pacjenci byli następnie oceniani za pomocą skali depresji Becka 1 (BDI)[23], skali depresji Hamiltona (HAM-D)[24] oraz skali lęku Hamiltona (HAM-A)[25]. Czas trwania choroby mierzono jako liczbę lat od początku pierwszego epizodu depresyjnego.

6.2.2.3 Analizy biochemiczne

U każdego uczestnika badania wykonano podstawowe oznaczenia z krwi – morfologia, stężenia potasu, sodu, kreatyniny, aminotransferaza alaninowa (ALT), aminotransferaza asparaginianowa (AST), CRP, hormon stymulujący

tarczycę (TSH), TC, lipoproteiny o niskiej gęstości (LDL), lipoproteiny o wysokiej gęstości (HDL), trójglicerydy (TGA).

Próbki moczu pobrano ze środkowego strumienia pierwszego porannego moczu i odwirowano przy 1300 x g przez 10 minut w temperaturze 4°C (MPW 351, MPW Med. Instruments, Warszawa, Polska). Supernatant zebrano, zamrożono i przechowywano w temperaturze -80°C w probówkach Eppendorfa do czasu przeprowadzenia analizy biochemicznej.

Wszystkie próbki były następnie jednocześnie badane. Oceniono następujące parametry: całkowita pojemność antyoksydacyjna (TAC), CAT, GPx, SOD, zredukowany glutation (GSH), całkowity status oksydacyjny (TOS), 3-nitrotyrozyna (3-NT), końcowe produkty zaawansowanej glikacji (AGE), produkty zaawansowanego utleniania białek (AOPP), N-formylokinurenina (NFKN), kinurenina (KN), tryptofan (TRY) i β-amyloid.

Wszystkie odczynniki do testów biochemicznych otrzymano z firmy Sigma-Aldrich. Fluorescencję/absorbancję mierzono przy użyciu multimodalnego czytnika mikropłytek Infinite M200 PRO, Tecan (Tecan Group Ltd., Männedorf, Szwajcaria). Wszystkie oznaczenia standaryzowano do 1 mg białka całkowitego.

6.2.2.4 Analiza statystyczna

Analiza statystyczna została przeprowadzona z użyciem języka R Statistical (wersja 4.1.1). Poziom istotności testów statystycznych w analizie ustalono na α=0,05. Testowanie zmiennych na skali ciągłej przeprowadzono za pomocą testu Shapiro-Wilka. Zastosowano dwa rodzaje testów: parametryczny (dla zmiennych o rozkładzie normalnym) i nieparametryczny (dla zmiennych o rozkładzie innym niż normalny). Wieloczynnikową analizę wpływu wybranych parametrów

klinicznych na czynnik depresji przeprowadzono za pomocą modelu regresji logistycznej, opartego na uogólnionym modelu liniowym. Szczegółowy opis metod wykorzystanych w analizie statystycznej znajduje się w pracy oryginalnej.

6.2.3 Wyniki

6.2.3.1 Charakterystyka grupy badanej

Analiza danych socjodemograficznych nie wykazała istotnych statystycznie różnic w wieku, płci i wskaźniku masy ciała (BMI) między grupą badaną a grupą kontrolną. Test *post hoc* wykazał istotnie większy odsetek pacjentów palących więcej niż 1 paczkę papierosów dziennie oraz niższy odsetek osób niepalących w grupie badanej w porównaniu z grupą kontrolną.

6.2.3.2 Analiza różnic w wynikach skal psychometrycznych oraz parametrów biochemicznych pomiędzy grupami.

Grupa chorych na depresję charakteryzowała się wyższymi średnimi stężeniami TGA w surowicy oraz SOD, 3-NT, CAT, GSH i TRY w moczu, oraz niższymi stężeniami HDL w surowicy. Wszystkie istotne różnice charakteryzowały się dużymi wielkościami efektu.

6.2.3.3 Analiza zależności pomiędzy wynikami skal psychometrycznych, poziomem badanych parametrów biochemicznych i czasem trwania choroby.

Wyniki skal psychometrycznych HAM-A, HAM-D i BDI oraz czynnik czasu trwania choroby wykazały istotne powiązania ze stężeniami HDL i TGA w surowicy krwi oraz stężeniami SOD, 3-NT, CAT i TRY w moczu. Stężenie GSH w moczu korelowało z wynikiem HAM-A. Wszystkie istotne korelacje charakteryzowały się dużymi wielkościami efektu. Zaobserwowano ujemną korelację z HDL — wyższy wynik w skalach HAM-A, HAM-D i BDI, podobnie

jak dłuższy czas trwania choroby, korelował ze spadkiem poziomu HDL. Wzrost wyników skal psychometrycznych i dłuższy czas trwania choroby korelował ze wzrostem poziomu TGA, SOD, 3-NT, CAT, TRY i GSH. Fakt, że prawie wszystkie wyniki kwestionariusza korelowały z tymi samymi parametrami, tłumaczy się tym, że wyniki kwestionariusza były między sobą silnie skorelowane ($r \geq 0,80$).

6.2.3.4 Analiza wielowymiarowa efektu parametrów biochemicznych na czynnik depresji

Do stworzenia modelu wykorzystano pięć predyktorów (HDL, TGA, SOD, 3-NT, GSH). Parametry TGA, SOD i GSH nie miały istotnego wpływu na czynnik depresji. Wzrost stężenia HDL o 1,00 mg/dl obniżał logarytm ilorazu szans wystąpienia depresji o 0,07 – przy założeniu, że kontrolowano inne predyktory. Zwiększenie stężenia 3-NT o 1,00 nmol/mg białka zwiększyło logarytm ilorazu szans wystąpienia depresji o 15,52. Z analizowanych danych wynika że pacjenci u których stwierdzono stężenie HDL < 40 mg/dl i stężenie 3-NT > 0,3 nmol/mg białka byli bardziej narażeni na wystąpienie depresji, podczas gdy pacjenci u których stwierdzono stężenie HDL > 80 mg/dl i stężenie 3-NT < 0,15 nmol/mg białka byli mniej podatni na wystąpienie depresji.

6.2.4 Wnioski

1. Populacja osób chorujących na depresję charakteryzuje się większym nasileniem stresu oksydacyjnego i nitrozowego w porównaniu do populacji zdrowej.
2. Marker stresu nitrozowego – 3-nitrotyrozyna (3-NT) – oznaczany w moczu, w połączeniu z lipoproteiną wysokiej gęstości (HDL) oznaczaną w surowicy może stanowić potencjalny marker depresji.

7. Zgoda Komisji Bioetycznej

Projekt badania został zaakceptowany przez Komisję Bioetyczną Uniwersytetu Medycznego w Białymstoku (zgoda nr RI-002/582/2019).

KOMISJA BIOETYCZNA
UNIWERSYTETU MEDYCZNEGO w BIAŁYMSTOKU
ul. Jana Kilińskiego 1
15-089 Białystok
tel. (085) 748 54 07, fax. (085) 748 55 08
prorektorkl@umb.edu.pl

Białystok, 19-12-2019

Uchwała nr: R-I-002/582/2019

Komisja Bioetyczna Uniwersytetu Medycznego w Białymstoku, po zapoznaniu się z projektem badania zgodnie z zasadami GCP/ Guidelines for Good Clinical Practice /- **w y r a ż a z g o d ę** na prowadzenie tematu badawczego: „Analiza profilu metabolomicznego i wybranych parametrów biochemicznych u chorych na depresję z cechami melancholii " przez lek. Aleksandra Nobisa wraz z zespołem badawczym z UMB.

Przewodnicząca Komisji Bioetycznej UMB

prof. dr hab. Otylia Kowal-Bielecka

8. Kopie publikacji wchodzących w skład rozprawy doktorskiej

Review

Peripheral Markers of Depression

Aleksander Nobis *[iD], **Daniel Zalewski**[iD] and **Napoleon Waszkiewicz**[iD]

Department of Psychiatry, Medical University of Bialystok, pl. Brodowicza 1, 16-070 Choroszcz, Poland;
daniel.zalewski@umb.edu.pl (D.Z.); psych@umb.edu.pl (N.W.)
* Correspondence: aleksander.nobis@umb.edu.pl

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Abstract: Major Depressive Disorder (MDD) is a leading cause of disability worldwide, creating a high medical and socioeconomic burden. There is a growing interest in the biological underpinnings of depression, which are reflected by altered levels of biological markers. Among others, enhanced inflammation has been reported in MDD, as reflected by increased concentrations of inflammatory markers—C-reactive protein, interleukin-6, tumor necrosis factor-α and soluble interleukin-2 receptor. Oxidative and nitrosative stress also plays a role in the pathophysiology of MDD. Notably, increased levels of lipid peroxidation markers are characteristic of MDD. Dysregulation of the stress axis, along with increased cortisol levels, have also been reported in MDD. Alterations in growth factors, with a significant decrease in brain-derived neurotrophic factor and an increase in fibroblast growth factor-2 and insulin-like growth factor-1 concentrations have also been found in MDD. Finally, kynurenine metabolites, increased glutamate and decreased total cholesterol also hold promise as reliable biomarkers for MDD. Research in the field of MDD biomarkers is hindered by insufficient understanding of MDD etiopathogenesis, substantial heterogeneity of the disorder, common co-morbidities and low specificity of biomarkers. The construction of biomarker panels and their evaluation with use of new technologies may have the potential to overcome the above mentioned obstacles.

Keywords: depression; biomarkers; inflammatory; interleukins; oxidative stress; brain-derived neurotrophic factor (BDNF); panels; melancholic; atypical

1. Introduction

Depression, or Major Depressive Disorder (MDD) is the most prevalent psychiatric disorder worldwide and a leading cause of disease burden [1]. It is mainly characterized by depressed mood, anhedonia, sleep and appetite disturbances, loss of interest or pleasure in activities once enjoyed and feelings of guilt or worthlessness. A high suicide rate among individuals suffering from the disorder is the darkest side of depression. Currently affecting around 300 million people worldwide and with 5%–17% of the population suffering from the disorder at least once in their lifetime, depression is a major clinical, emotional and socioeconomic burden for society. The World Health Organization (WHO, Geneva, Switzerland) estimates that, by 2030, depression will have become the leading cause of disability worldwide [2]. An important issue in depression is that of low remission rates. Only approximately half of the patients achieve complete remission [3] and with each subsequent treatment remission rates decrease [4]. The efficacy of classical antidepressant drugs, which target the monoamine systems, is only marginally higher than that of a placebo [5]. An urgent need exists to find biomarkers in order to better understand the pathogenesis of depression, monitor treatment outcomes and identify new drug targets [6]. The aim of the study was to provide a comprehensive review of potential depression markers. For some, currently available evidence is insufficient to allow for regarding of them as biomarkers sensu stricto. However, alterations in their concentrations may

provide relevant information concerning the pathophysiology of depression and be a starting point for future, larger biomarker studies.

1.1. Concepts of Depression

The etiopathogenesis of depression is highly complex and therefore still not fully understood. Although the monoaminergic theory of depression is now universally accepted, other pathologies have also been found to be associated with the development of the condition. Research to date has focused mainly on stress axis dysregulation (hypothalamus–pituitary–adrenal, HPA), oxidative stress-induced damage [7–10], hippocampal and frontal lobes dysfunction (neurodegeneration) [11,12], and neurotoxic, inflammatory and immunological processes [7,13–17]. In recent years, knowledge of genetic and epigenetic factors which could contribute to depression has expanded. Furthermore, many psychological hypotheses seek to explain the causes of depression (e.g., learned helplessness hypothesis) [18]. Finally, the neurodevelopmental theory of depression attempts to combine previous approaches with particular emphasis on the impact of the earliest stages of a person's life on MDD occurrence [19].

1.2. Heterogeneity of Depression

Depression is a heterogeneous disorder. To date, no universally accepted classification of depression subtypes has been developed. Most authors acknowledge the existence of melancholic and atypical subtypes [20], but others also mention the following subtypes: dopamine-related subset with anhedonia, inflammatory subset [21], the existence of which is questioned by others [22], suicidal depression [23], anxious depression, depression with functional and somatic traits (closely related to chronic fatigue syndrome) [24], reactive depression, psychotic depression, dysthymia [11], depression with panic attacks, depression in people with obsessive traits, depression accompanying a known physical illness, and pseudo-demented depression [25]. According to some authors, MDD should not be regarded as a single disease but rather a group of diseases with distinct causes, patho-physiologies and symptomatologies [11,26].

1.3. Diagnosis of Depression

The diagnosis of depression is currently symptom-based. There are several psychometric scales which help clinicians to assess different dimensions of depressive functioning, of which the most commonly used are the Hamilton Depression Rating Scale (HDRS) [27], Montgomery-Asberg Depression Rating Scale (MADRS) [28] and Beck Depression Inventory [29]. The International Classification of Diseases (ICD) (from the 6th to the 11th edition) and the Diagnostic and Statistical Manual (DSM) (from I to V edition) provide a set of criteria for diagnosing depression. However, they are based on the patient's self-reports and the clinician's observations of patient behaviour [30]. Neither DSM nor ICD makes reference to any objective, measurable biological features that could assist in diagnosing depression. This makes the entire diagnostic process subjective, to a certain degree, and leads to a considerable risk of misdiagnosis and suboptimal treatment, which may last for many years. By way of illustration, bipolar disorder (BPD) in its depressive phase is frequently misdiagnosed as MDD [31]. Furthermore, depressive symptomatology cannot be clearly understood and properly codified in psychiatric classifications without a thorough knowledge of the neurobiological, pharmacological and etiological mechanisms underlying the development of depression [9]. Another important issue is the contradictory character of several symptoms of depression in DSM (e.g., increased or decreased body mass or appetite, hyper- or hyposomnia, decreased or increased activity). A few distinct or even opposite clinical pictures can be built based on these criteria. Hence, the use of 'depression' as an umbrella term could lack biological validity [32,33]. Additionally, the discovery of objective, biological markers of depression would not only be an invaluable help for clinicians but could also serve as a springboard for improving our understanding of the biology of depression with its various subtypes.

1.4. Biomarker Subtypes

A biomarker is defined as a characteristic that can be objectively measured and evaluated as an indicator of physiological processes, pathogenic processes or responses to a therapeutic intervention [34]. Markers should not be confounded with characteristics of a particular disease [35]. There are several classifications of biomarkers described in the literature. For the purposes of this review, we adopted (with modifications) a classification proposed by Lopresti et al. [23] presented in Figure 1. Biomarkers can be divided into diagnostic biomarkers, which are used to confirm the presence or absence of disease; treatment biomarkers, which could be helpful in selecting optimal treatment for a particular patient from a range of available therapeutic options; treatment–response biomarkers (also called mediators) to measure treatment progress; prognostic biomarkers to predict disease course; and, finally, predictive biomarkers, whose role is to predict the future onset of disease [23]. Biomarkers can also be classified as trait, state and endophenotype biomarkers [36]. Trait biomarkers are those which can be observed continuously—not only in the acute phase of the disease, but also in remission or even before disease onset. The last characteristic makes them similar, to a certain degree, to predictive biomarkers. Trait biomarkers may help identify vulnerable individuals. State biomarkers reflect the current clinical status of the patient. They are present during the acute phase of the disease or shortly before disease onset, but they disappear in remission. Endophenotype biomarkers are useful in subtyping depression. They are based on the relationship between depressive phenotypes and specific genetic factors [36].
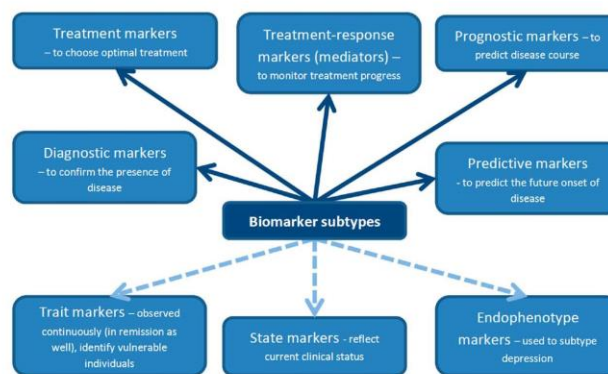

Figure 1. Biomarkers can be divided into several subtypes according to their function (top half of the figure, solid lines) or based on when they can be observed (bottom half of the figure, dashed lines).

Biomarkers should be highly sensitive and disease-specific (>80%) to be clinically useful [37]. Receiver operating characteristic area under the curve (ROC AUC) is a measure of biomarker accuracy, with ROC AUC < 0.5 suggesting poor accuracy, and ROC AUC close to 1 suggesting high accuracy [38].

1.5. Biological Systems Affected in Depression

In depression, as evidence to date suggests, five biological systems are mainly affected. Therefore, they constitute natural sources of potential biomarkers. These are the inflammatory, neurotransmitter, neuroendocrine, neurotrophic and metabolic systems (Figure 2) Each system can be assessed at different biological levels (this is called the 'omics' approach)—from genomic and epigenomic, through transcriptomic and proteomic to metabolomic (Figure 3). It is worth emphasizing that not every technique is equally efficient in the evaluation of a particular system. Apart from the 'omics' mentioned above, there is a growing understanding of the human microbiome and its impact on mental health. Therefore, its assessment might help establish a more accurate diagnosis and provide more appropriate treatment for depression [39].
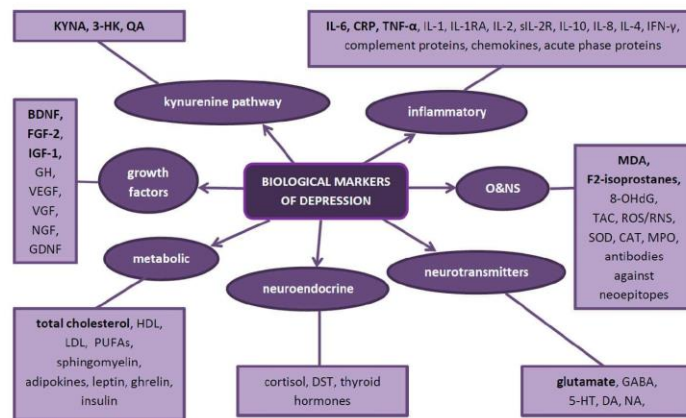
Figure 2. The summary of the most important depression markers. **In bold**—those confirmed by a recent umbrella meta-analysis [40]. Abbreviations: 3-HK—3-hydroxykynurenine; 5-HT—serotonin; 8-OHdG—8-hydroxy-2-deoxiguanosine; BDNF—brain-derived neurotrophic factor; CAT—catalase; CRP—C-reactive protein; DA—dopamine; DST—dexamethasone suppression test; FGF-2—fibroblast growth factor-2; GABA—gamma-aminobutyric acid; GDNF—glial cell line derived neurotrophic factor; GH—growth hormone; HDL—high-density lipoprotein; IGF-1—insulin-like growth factor-1; IL-1—interleukin-1; IL-2—interleukin-2; IL-4—interleukin-4; IL-6—interleukin-6; IL-8—interleukin-8; IL-10—interleukin-10; IL-1RA—interleukin-1 receptor antagonist; INF-γ—interferon-γ; KYNA—kynurenic acid; LDL—low-density lipoprotein; MDA—malonylo-dialdehyde; MPO—myeloperoxidase; NA—noradrenaline; NGF—nerve growth factor (NGF); O&NS—oxidative and nitrosative stress; PUFAs—polyunsaturated fatty acids; QA—quinolinic acid; ROS/RNS—reactive oxygen/nitrogen species; sIL-2R—soluble interleukin-2 receptor; SOD—superoxide dismutase; TAC—total antioxidant capacity; TNF-α—tumor necrosis factor-α; VEGF—vascular endothelial growth factor; VGF—VGF nerve growth factor.
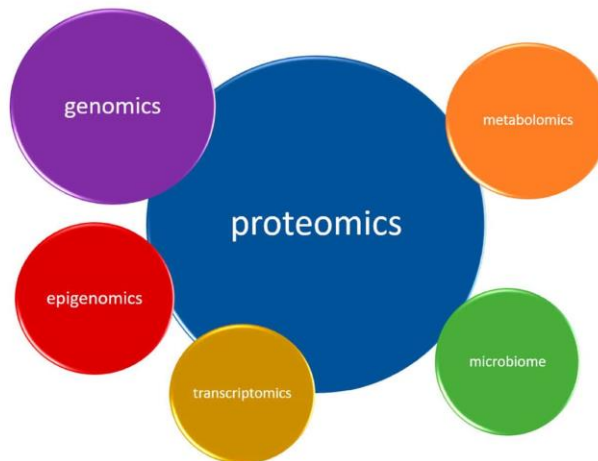

Figure 3. Biological systems involved in depression can be assessed on different measurement 'levels', called 'omics'. Note that every system can theoretically be assessed on each 'omic' level.

2. Methods

A literature search was conducted in PubMed, Scopus and Web of Science databases using keywords: 'depression', 'biomarker', 'marker', 'proteomic', 'metabolomic', 'inflammatory', 'growth factors', 'cytokines', 'kynurenine', 'oxidative stress', 'genetic', 'subtypes', 'melancholic', 'biosignature' as well as combinations of these terms. Relevant articles were then included with the intention to cover the widest possible spectrum of different markers for depression.

3. Inflammatory Findings in Depression

The link between inflammation and depression has been conclusively proven and widely reviewed [13,41,42]. In approximately 30% of patients with MDD, the inflammatory response is disturbed [43] and patients with inflammatory disorders have higher depression rates. The distribution of inflammatory markers elevation in a depressive population is continuous and does not allow for distinguishing a distinct inflammatory subtype of depression [22].

Chronic, low grade inflammation is the way through which behavioral and social variables impact health [44]. Depression is associated with chronic low-grade inflammation and is compared to a chronic cold [15]. Patients suffering from autoimmune and atopic disorders, metabolic syndrome, obesity, tobacco dependence, dental caries, atherosclerosis—all of which are associated with increased inflammation—are at a higher risk of depression (Berk et al., 2013). Inflammation is described as a major mediator in the development of MDD and the metabolic syndrome [45]. However, mild chronic inflammation is only a general concept which does not adequately explain the pathophysiology of depression [46].

While it is unlikely that depression is simply an inflammatory disorder, enhanced activation of the immune system in individuals with depression is not merely coincidental. There is substantial evidence confirming the involvement of inflammatory factors in the pathogenesis of depression [47–52]. Inflammation is present not only during depressive episodes—elevated levels of inflammatory factors significantly contribute to the occurrence of the first depressive episode [53–55]. Physiological and psychological stress, the most important risk factor for depression, has been proven to cause an immune challenge for the body and provoke an inflammatory response [56,57]. Smoking and obesity are common in depression [58,59] and can influence the concentration of inflammatory markers [60,61]. Continuous elevation of cytokines leads directly to increased levels of cortisol by stimulating the HPA axis and increasing corticotropin-releasing hormone (CRH) production [48] and, indirectly, by inducing glucocorticoid resistance, to neurotransmitter concentration changes which are interpreted by the brain as stressors [62,63]. Additionally, elevated cytokine levels cause an increase in the expression of serotonin transporter and induce indoleamine 2,3-dioxygenase (IDO) activity, thus enhancing the kynurenine pathway in the brain. All these factors contribute to the development of depression [64]. Increased inflammation leads to cognitive decline and is likely to be responsible for the impairment of cognitive function observed in depression [65].

The pro-inflammatory state, reflected by elevated levels of pro-inflammatory cytokines, manifests itself externally in what is termed 'sickness behaviour', characterized by anhedonia, weight loss, anorexia, memory dysfunction and impaired social interaction—symptoms that occur in MDD [66]. Central or peripheral administration of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interferon-γ (INF-γ) or tumor necrosis factor-α (TNF-α), may produce sickness behaviour [67–71].

The presence of inflammation, however, is not specific to MDD and could be an indicator of two other major psychiatric disorders: schizophrenia and BPD, indicating the possibility of common underlying pathogenetic pathways in disorders involved in immune dysfunction [72,73]. Dubois et al. [72] found that levels of inflammatory biomarkers are similarly elevated in all three disorders and are more closely related to their stage and severity than to a particular disease. Variations in cytokine concentrations could also predict the risk of disease occurrence and treatment resistance in the above mentioned conditions.

Danese et al. [73,74] revealed that people who were subjected to maltreatment or abuse in their childhood were more prone to developing depression in adult life, which may be associated with a predisposition to prolonged stress reactions (HPA axis dysregulation) and stronger inflammatory responses in these individuals. Interestingly, a similar effect—a higher risk of depression—was observed in adults who suffered from a serious illness in their childhood [75].

Since 1980s, with new discoveries emerging in the field of biological psychiatry, there has been a controversy over whether depression is characterized by immune activation or immune suppression. Both hypotheses were supported by convincing evidence. The lowered lymphocyte transformation test (LTT) [76] and blunted natural killer cell activity (NKCA) [77] in depressive patients indicate immunosuppression. At the same time, a large body of evidence supported the role of immune activation in depression—enhanced levels of pro-inflammatory cytokines and acute phase proteins were observed, together with immune cells activation [7,13–17].

To cut the Gordian knot, Maes and Carvalho [78] proposed a concept of two opposite systems which act simultaneously in depression and counter-regulate each other: the immune-inflammatory response system (IRS) and the compensatory immune-regulatory reflex system (CIRS). Both of them are closely interrelated—the activation of IRS inevitably entails the activation of CIRS and the activated CIRS opposes the inflammatory action of IRS. This interplay ultimately leads to the extinction of the inflammatory response, which could be responsible for the self-limiting character of depression. However, following the first depressive episode, once IRS and CIRS have been activated for the first time, there is no return to the homeostatic status quo, and subsequent episodes are characterized by a sensitized immune response, which could explain why successive depressive episodes frequently occur without a tangible cause and are more severe. Greater severity of MDD has been linked to increased activation of both IRS (neopterin, sIL-6R) and CIRS (sTNF-α, sIL-1RA, IL-10) [78]. The pro-inflammatory cytokine IL-6 (IRS) enhances the production of anti-inflammatory sIL-1RA, IL-10 and glucocorticoids (CIRS) [79,80]. Haptoglobin—an acute phase protein—has anti-inflammatory effects and acts as an antioxidant [81]. An increase in IL-1β in depression (M1 activation) is accompanied by an increase in soluble IL-1 receptor antagonist (sIL-1RA) (reflex inhibition). A precise description of IRS and CIRS is beyond the scope of this review and can be found in a publication by Maes and Carvalho [78]. The main conclusions from this paper are presented in Table 1 [78].

Table 1. The main compounds of immune–inflammatory response system and compensatory immune–regulatory reflex system. Abbreviations: IL-1β—interleukin-1β; IL-2—interleukin-2; IL-4—interleukin-4; IL-6—interleukin-6; IL-10—interleukin-10; IL-1RA—interleukin-1 receptor antagonist; sIL-2R—soluble interleukin-2 receptor; sTNF-R1—soluble tumor necrosis factor receptor 1; sTNF-R2—soluble tumor necrosis factor receptor 1; TNF-α—tumor necrosis factor-α.

IRS	CIRS
IL-1β	sIL-1RA
TNF-α	sTNF-R1, sTNF-R2
IL-2 signaling	IL-2, sIL-2R
IL-6 trans-signaling	IL-6 classical signaling
Th1 and Th17 lymphocyte activation	Th2 lymphocyte activation with IL-4 production, Treg lymphocyte activation with IL-10 production
M1 macrophagic activation	

Many antidepressant drugs have anti-inflammatory properties which could partly explain their efficacy in the treatment of depression [82]. Antidepressants reduce the production of pro-inflammatory cytokines and increase concentrations of anti-inflammatory cytokines. In a recent meta-analysis, antidepressant treatment was found to attenuate IL-1B, IL-6 and IL-10 levels as well as M1 polarization of macrophages [83]. Interestingly, an inverse relationship was also observed: anti-inflammatory drugs such as celecoxib, ibuprofen or TNF-α blocker infliximab were described as having antidepressant properties [84–86].

Among inflammatory markers, IL-6, C-reactive protein (CRP), TNF-α and soluble interleukin-2 receptor (sIL-2R) appear to have the greatest potential to serve as markers for depression.

3.1. Interleukin-6

3.1.1. As a Diagnostic Biomarker

Among all inflammatory cytokines, an increased concentration of IL-6 is probably the most widely and consistently reported in depression. This relationship has been confirmed by several meta-analyses [40,42,47,53,83,87–90]. Increased IL-6 could be an early marker for cognitive decline in depression. It also corresponds to depression severity and increased HPA axis activity [91–93]. Kunugi et al. [21] proposed the use of cerebro-spinal fluid (CSF) IL-6 levels as a bio-marker for the neuro-inflammatory subtype of MDD.

3.1.2. As a Treatment–Response Biomarker

Apart from being a potential diagnostic (state) biomarker, IL-6 has potential to serve as a treatment-response biomarker. Levels of IL-6 decrease along with successful antidepressant treatment [83], which could suggest that antidepressants have anti-inflammatory properties. Decreased levels of leukocytic mRNA for IL-6 have been correlated with effective treatment [94] while persistently elevated serum IL-6 concentrations seem to be characteristic of treatment-resistant depression (TRD) [79]. Interestingly, electroconvulsive therapy (ECT) is reported to increase IL-6 levels [95]. In a meta-analysis by Hiles et al. [88], higher baseline IL-6 levels were correlated with a more significant decrease in depressive symptoms following antidepressant treatment. Furthermore, a meta-analysis by Strawbridge et al. [96] demonstrated that IL-6 levels decrease along with antidepressant treatment administration, regardless of the outcome.

3.1.3. IL-6 Trans-Signaling

IL-6 can exert its biological activity via two separate signaling pathways—the classical pathway and trans-signaling. In the classical pathway, IL-6 binds to membrane-bound IL-6 receptor (IL-6R), present on a few cell types in the body. Elevated levels of pro-inflammatory cytokines may cause cleavage of IL-6R from the cell surface into the bloodstream. The activation of soluble IL-6 receptors (sIL-6R) is responsible for IL-6 trans-signaling [44], which is characteristic of inflammation, while IL-6 classic signaling contributes to anti-inflammatory effects [97]. To assess the impact of IL-6 on the body, it is crucial to measure both IL-6 and sIL-6R concentrations. Elevated sIL-6R levels combined with higher IL-6 concentrations indicate enhanced IL-6 trans-signaling, and thus enhanced inflammation [83,98–100]. A study by Maes et al. reported elevated sIL-6R levels in depression [80]. Further studies specified that enhanced IL-6 trans-signaling is characteristic of an acute (current) depressive episode (melancholic or atypical) compared to a remitted state and is a distinctive feature of TRD and melancholia [80,99,100].

3.2. C-Reactive Protein

3.2.1. As a Diagnostic Biomarker

CRP is the most frequently used marker of inflammation. CRP is produced in the liver and its secretion is stimulated by IL-6 [44]. The majority of studies have demonstrated that CRP levels are elevated in depression [22,40,42,47,89,96], although no causal relationship has been established between an enhanced CRP concentration and depression [101]. A subgroup analysis revealed that higher CRP levels may be characteristic of depressed men [102–104], atypical depression [105], depression with somatic symptoms [106], depressed patients with a history of childhood trauma [107] and cumulative depressive episodes [108]. Elevated CRP levels have also been suggested to be more specific for female

than for male patients with MDD [109]. However, it should be noted that enhanced CRP levels are not specific to depression—they are also present in euthymic BPD and manic episodes [110].

3.2.2. As a Predictive Biomarker

CRP also shows potential as a predictive biomarker. Pasco et al. [54] reported that high sensitivity CRP (hsCRP)—a more sensitive measure of inflammation—is an independent risk factor of depression and its elevated levels can predict de novo MDD occurrence. These findings were confirmed in a meta-analysis by Valkanova [89]. Higher CRP concentrations have been linked to an increased risk of hospitalization due to depression [111].

3.2.3. As a Prognostic Biomarker

In the majority of studies, low baseline CRP levels were found to be associated with a better and faster response to selective serotonin reuptake inhibitor (SSRI) treatment [109,112,113]. However, the results are inconsistent. According to some studies, higher baseline CRP levels could predict a better response to treatment [88,114], whereas in other studies they are reported to have no impact on treatment results [115].

3.2.4. As a Treatment Biomarker

Altered CRP levels may help clinicians select an optimal treatment strategy for a particular patient since high baseline CRP levels predict a better response to pharmacotherapy in comparison to psychological therapy [116]. When it comes to drug selection, altered CRP levels might predict the outcome of treatment with escitalopram and nortriptyline (with opposite effects) [112]. Antidepressant treatment reduces CRP concentration marginally [88].

The production of CRP in the liver is induced by TNF-α. Depressive patients with higher baseline CRP levels show a more significant improvement following the injection of an anti-TNF-α drug, infliximab [117].

Most studies investigating inflammatory markers of depression have focused on CRP and IL-6. This approach, however, is too narrow and does not address the complexity of immune-inflammatory processes involved in the pathophysiology of MDD. It would be desirable to simultaneously evaluate as many inflammatory markers as possible and correlate them with a comprehensive clinical assessment in order to understand the complex network of interactions between them (interactomic approach) [118,119].

It is noteworthy that some depressive patients may have elevated CRP and IL-6 levels, even in the absence of inflammation [44].

3.3. Tumor Necrosis Factor-α

3.3.1. As a Diagnostic Biomarker

Tumor Necrosis Factor-α is another inflammatory cytokine, constantly and repeatedly reported to be increased in depression as compared to healthy controls [22,40,53,87,90,96,98]; however certain meta-analyses found this to be inconclusive [42,120]. Moreover, number of depressive episodes is associated with increased TNF-α concentrations [121].

3.3.2. As a Diagnostic Biomarker

Baseline levels of TNF-α are not associated with a subsequent response to treatment [115]. Antidepressant treatment significantly decreases TNF-α concentrations, but only in responders. Persistently elevated levels of TNF-α during the course of treatment are associated with poorer outcomes, thus identifying patients with TRD [96,122]. Similar effects have been reported for electroconvulsive therapy (ECT)—clinical improvement following electroconvulsive therapy (ECT) correlated with a decline in TNF-α concentrations [123]. Hence, TNF-α could be a valuable marker of treatment resistance (a treatment-response marker) and a potential new biological target for the

pharmacotherapy of depression. Anti-TNF-α drugs (infliximab, etanercept) have previously been reported to attenuate depressive symptoms [117].

3.3.3. TNF Receptors

The inflammatory effect of TNF-α is mediated by its receptors—TNF-R1 and TNF-R2, both of which are expressed on cell surfaces. However, under certain conditions, they can be released into plasma. Once released, they are no longer active and act as 'decoy' receptors, binding circulating TNF-α molecules and thus regulating TNF-α signaling [124]. Depression is characterized by elevated serum TNF receptor levels, which are regarded as state [78] or trait [125] biomarkers.

Interestingly, Jannelidze et al. [126] demonstrated that IL-6 and TNF-α are elevated in patients at an increased risk of suicide, indicating that they may be regarded as state biomarkers. It has also been proven that the two cytokines directly inhibit adult hippocampal neurogenesis [127].

3.4. Interleukin-1

IL-1β is one of the major pro-inflammatory cytokines and together with TNF-α and a few other cytokines is thought to be responsible for the occurrence of sickness behaviour. A central or peripheral injection of IL-1β produces such a behaviour in mice. Interestingly, a similar effect has been described for lipopolysaccharide (LPS, endotoxin)—an injection of endotoxin leads to ventral striatum deactivation, diminished reward processing and anhedonia [128–130]. An increase in IL-1β in depression remains controversial. Certain meta-analyses support it [46,120] while others do not indicate such an association, including a recent umbrella review conducted by Carvalho et al. [89,90]. Such discrepancies may be caused by increased body mass index (BMI), which contributes to an increase in IL-1β [89], or the fact that IL-1 concentrations increase with the number of depressive episodes [121]. Conversely, Talarowska et al. [131] did not find significant differences in IL-1 concentrations between patients suffering from their first or successive depressive episodes. IL-1 also holds promise as a potential prognostic biomarker since elevated levels of IL-1β mRNA in blood can predict a poorer response to antidepressant treatment [132].

IL-1, TNF-α and IL-6 exert their pro-depressive effects by inhibiting neurogenesis [127,128], inducing apoptosis [129,130], negatively affecting synaptogenesis, synaptic plasticity and connectivity as well as the structure of synaptic membranes [131,132].

3.5. Interleukin-1 Receptor Antagonist

IL-1 receptor antagonist (IL-1RA) is a protein which competes with IL-1, binding to IL-1 receptor. Its production is stimulated by pro-inflammatory agents (e.g., IL-6) and therefore, elevated levels of IL-1RA indicate an enhanced inflammatory response. However, IL-1RA itself actually inhibits IL-1β and IL-1α signaling and as such is part of CIRS [35,79]. Some studies have reported that IL-1RA is elevated in depression [90,98], but no such association was found in a recent umbrella review by Carvalho [40]. Soluble IL-1RA is elevated both in unipolar depression and BPD, which excludes it as a marker for differentiating between these two disorders. It remains elevated even in affective remission and therefore it may be perceived as a trait biomarker for depression [125]. Sowa-Kućma et al. [100] demonstrated that sIL-1RA was positively correlated with a number of hospitalizations due to depression within a year, before being tested in affected individuals.

3.6. Interleukin-2, Soluble Interleukin-2 Receptor

IL-2 is a key cytokine in T lymphocytes activity [133,134], the function of which is disturbed in depression [135]. The effects of IL-2 are mediated by IL-2 receptor (IL-2R), present on cell membranes of activated T cells. IL-2R may also be cleaved into the bloodstream. It has been reported by a number of authors that soluble IL-2R (sIL-2R) is elevated in the blood of patients with depression and BPD [40,87,90,98]. Plasma sIL-2R could serve as a surrogate marker of T lymphocyte activation and IL-2

production [78]. sIL-2R may have immune-suppressant, immune-regulatory or immune-stimulatory properties, although most studies describes it as immune-suppressant [136].

3.7. Interleukin-10

Interleukin-10 (IL-10) is one of the most important anti-inflammatory cytokines. Elevated IL-10 concentrations in blood, along with enhanced IL-4 levels, may play a role in regulating IRS. In a meta-analysis performed by Kohler et al. [90], elevation of IL-10 was associated with depression. Two other meta-analyses found that IL-10 concentrations decrease with antidepressant treatment, making it a promising marker of treatment efficacy [83,88]. No differences in IL-10 concentrations between the first and subsequent depressive episodes were noted [137].

3.8. Interleukin-8

Data regarding IL-8 concentrations in depression are inconsistent. It has been reported that IL-8 is elevated in severe depression and positively correlated with depressive symptoms [138], which could suggest its role as a state marker. However, a meta-analysis by Eyre et al. [139] did not establish significant differences in IL-8 concentrations between patients with MDD and healthy controls. Lower baseline IL-8 levels were associated with a better response to antidepressant treatment in a recent meta-analysis [122], thus supporting its role as a prognostic biomarker.

3.9. Interleukin-4

Interleukin-4 (IL-4), one of the most important anti-inflammatory cytokines, was recently found to be downregulated in depression in a meta-analysis by Osimo [22]. IL-4 is produced by Th2 lymphocytes. IL-4 increases the production of anti-inflammatory sIL-1RA and inhibits M1 macrophage polarization, thus decreasing the release of IL-1β, IL-6 and TNF-α, as such contributing to CIRS [78].

3.10. Interferon-γ

INF-γ is a pro-inflammatory cytokine produced by Th1 lymphocytes. It is indicated that it causes microglial activation (shift) which contributes to depression [140]. Udina et al. [141] reported a higher risk of depression in patients treated with interferon for hepatitis C. As many as 40% of cancer or hepatitis C patients treated with INF-γ develop depressive symptoms and present with increased IL-6 levels. In depressed patients undergoing INF-γ therapy, lower tryptophan (TRP) and serotonin (5-HT) levels and higher kynurenine levels were noted in the peripheral blood [142–144]. Interestingly, the Combining Medications to Enhance Depression Outcomes (CO-MED) trial demonstrated a decrease in INF-γ after antidepressant treatment, which correlated with a lack of remission [145].

3.11. Macrophage Migration Inhibitory Factor

Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine that plays a role in hippocampal neurogenesis in animal models [146]. Decreased or elevated MIF levels have been reported in patients with MDD [147,148].

3.12. Transforming Growth Factor-β

Transforming growth factor-β (TGF-β) was analyzed in several studies as a potential marker for depression. However, recent meta-analyses did not prove significant changes in TGF-β levels in patients with MDD [40,90].

3.13. Other Cytokines

There are single reports in the available meta-analyses concerning increased concentrations of other cytokines—interleukin-3 (IL-3), interleukin-12 (IL-12), interleukin 13 (IL-13) and interleukin 18 (IL-18) [22,90]. However, their exact role and importance remains to be elucidated.

In a meta-analysis performed by Osimo et al. [22], three biomarkers, CRP, IL-12 and sIL-2R, presented significantly lower variability in patients with MDD compared to healthy controls.

3.14. Chemokines

Monocyte Chemoattractant Protein-1/Chemokine ligand 2 (MCP-1/CCL2) is responsible for the chemoattraction of monocytes, dendritic cells and memory T cells to the site of inflammation. Higher concentrations of this chemokine were found in depressed patients in comparison to healthy controls in a meta-analysis [139].

Furthermore, higher levels of eotaxin prior to antidepressant treatment, compared to its concentration following treatment, correlated with clinical remission [145].

3.15. Complement Proteins C2 and C3

The activity of complement is disturbed in depression. Levels of acute phase protein complement C3 are elevated in depression and are significantly higher in the atypical subtype compared to melancholic depression [149–151].

3.16. Bone Inflammatory Markers

Depressive patients have decreased bone mineral density and thus altered levels of bone inflammatory markers—osteo-protegerin (OPG)-RANK-RANKL system and osteo-pontin (OPN). Ketamine—a recently discovered fast-acting antidepressant agent—corrects these abnormalities [152].

3.17. Acute Phase Proteins

Depression has been associated with disturbances in acute phase proteins (APP): ceruloplasmin, inter-alpha-trypsin inhibitor heavy chain H4 and complement component—1qC [153]. Haptoglobin has also been reported to be elevated in depression and to differentiate between depressive subtypes [14]. Depression has also been associated with increased plasma B2-microglobulin [154].

3.18. Erythrocyte Sedimentation Rate

Erythrocyte Sedimentation Rate (ESR) is a non-specific measure of inflammation. In rheumatoid arthritis (RA) patients who were also diagnosed with depression, higher ESR levels were observed compared to non-depressive RA patients [155].

There is substantial heterogeneity in results in depression–inflammation studies. Even meta-analyses reveal contradictory results. Hiles et al. [156] searched for sources of inconsistency in depression–inflammation studies. The main confounding issues identified were the following: accuracy of MDD diagnosis, BMI and comorbid illnesses. A meta-analysis by Kohler et al. [90] added age and smoking status to the list.

3.19. Neopterin

Neopterin, a marker of cellular immune system activation, was reported to be upregulated in depression in some studies, particularly in the melancholic subtype. Neopterin also allows for estimation of the extent of oxidative stress (its concentration rises along with an increase in ROS levels) and the extent of Th1 lymphocytes activation [23]. A positive response to ECT is associated with a decrease in neopterin levels in responders [157] and a reduction in the neopterin:biopterin ratio [158]. Every subsequent episode of depression is associated with a more substantial increase in the level of neopterin, serving as an episode number marker [159].

The summary of the results of meta-analyses investigating inflammatory markers observed in depression is presented in Table 2.

Table 2. Summary of inflammatory markers in depression according to meta-analyses performed throughout the years (left to right). Abbreviations: D—downregulated; U—upregulated; —unchanged; CCL2—chemokine ligand 2; CRP—C-reactive protein; IL-1β—interleukin-1β; IL-3—interleukin-3; IL-4—interleukin-4; IL-6—interleukin-6; IL-10—interleukin-10; IL-12—interleukin-12; IL-13—interleukin-13; IL-18—interleukin-18; IL-1RA—interleukin-1 receptor antagonist.

	Howren 2009 [47]	Dowlati 2010 [53]	Liu 2012 [87]	Valkanova 2013 [39]	Haapakoski 2015 [42]	Strawbridge 2015 [96]	Goldsmith 2016 [98]	Kohler 2017 [90]	Ng 2018 [120]	Osimo 2020 [22]	Carvalho 2020 [40]
IL-6	U	U	U	U	U	U	U	U	U	U	U
CRP	U			U	U	U	U	U	-	U	U
TNF-α		U	U	U	-	U	U	U	U	U	U
sIL-2R		-				U		-		U	U
IL-1β	U	-			-			-	U		
IL-1RA							U		U		
IL-10		-					U	U			
IL-12							U	U		U	
IL-13								U			
IL-18								U		U	
TNF-R2								U		U	
CCL2										U	
IL-3										U	
IL-4		-						-		D	
INF-γ		-						D			

4. Oxidative & Nitrosative Stress Findings in Depression

The brain is particularly vulnerable to oxidative and nitrosative stress (O&NS) [160]. The hippocampus, cerebellar granule cells and amygdala are brain parts most susceptible to oxidative damage [161]. Psychological stressors induce cytokine production and an inflammatory response [162] which facilitates the generation of reactive oxygen and nitrogen species (ROS/RNS), leading to a pro-oxidant state. Clinical depression is accompanied by increased O&NS and impaired antioxidant status (e.g., lower TRP, tyrosine, albumin, zinc) [163]. Oxidative and nitrosative stress manifests itself, inter alia, by higher levels of mitochondrial reactive oxygen species, lipid peroxidation products, DNA and protein damage products [10]. Elevated levels of protein carbonyls reflect protein damage—8-hydroxy-2-deoxiguanosine (8-OHdG) and 8-oxo-7,8-dihydroguanosine (8-oxo-Gua) are markers of DNA and RNA damage, respectively while malonylo-dialdehyde (MDA) and F2-isoprostanes emerge as the effect of lipid peroxidation [164].

Oxidative and nitrosative stress products have been detected in peripheral blood, red blood cells (RBC), mononuclear cells, urine, CSF and postmortem brain tissue of depressed patients. It is not clear if O&NS in depression originates from the peripheral or central nervous system. There are, however, some indicators which could suggest its peripheral origin [163]. In rats with genetic susceptibility to depression, higher depression rates were observed after exposure to oxidative stress [165].

Antidepressant drugs have antioxidant properties which are thought to account for, at least partially, their antidepressant efficacy [166]. Interestingly, antioxidants are also described as having antidepressant properties [167].

Reactive oxygen species (ROS) are mainly generated in mitochondria as a side product of the respiratory chain. They destroy defense systems when overproduced, creating a vicious circle and enabling further ROS generation [168]. It is not clear how exactly ROS exert their detrimental impact on the brain. ROS overproduction is known to trigger pathological cascades, eventually leading to increased permeability of the blood-brain barrier, morphological changes in the brain and neuroinflammation [169]. Under pathological conditions, oxidative stress could also induce neurodegeneration via different mechanisms such as apoptosis, axonal damage and excitotoxicity [170].

Oxidative stress activates inflammatory pathways, as extensively reviewed by Moylan et al. [163], whereas inflammation increases oxidative stress (e.g., an increase in the levels of cytokines IL-1 and IL-6 leads to decreased levels of albumin, zinc and high-density lipoprotein—HDL) [171–174]. Among oxidative stress markers, lipid peroxidation markers appear to have the greatest potential in depression.

4.1. Total Antioxidant Capacity

Total antioxidant capacity (TAC) was found to be decreased in patients with MDD [164] and inversely correlated with severity of depression [175]. TAC did not increase in response to treatment or in remission [176], which suggests that TAC could be a trait biomarker for depression.

4.2. Peroxide

Elevated peroxide levels were confirmed in the sera of patients with MDD in a meta-analysis [164]. Maes et al. [177] found that peroxide levels are higher in the acute phase of MDD, but normalize if depression is long-lasting, which makes them potential state markers for MDD.

4.3. Nitric Oxide

L-arginine–NO pathways play a role in the pathophysiology of MDD and are altered by antidepressants [178,179]. The NO-producing enzyme, nitric oxide synthase (NOS), has two isoforms: neuronal NOS (nNOS), mainly involved in neurotransmission, and cytokine-inducible NOS (iNOS), which plays an important role in inflammation [180]. NO levels are higher in patients with MDD [181] and were reported to characterize depressive patients after suicide attempt [182], which could make them state markers and enable early identification of patients at risk of suicide. NO is also reported to be

involved in the pathogenesis of INF-γ-induced depression [183]. The disease is associated with lower NO metabolite levels and decreased platelet-endothelial NO activity [184]. However, a meta-analysis performed by Jimenez-Fernandez et al. [185] did not confirm significant differences in total nitrites in patients with MDD as compared to healthy controls. Nevertheless, another meta-analysis published by Liu et al. [164] documented decreased serum nitrate following antidepressant therapy.

4.4. Superoxide Dismutase

Superoxide dismutase (SOD) is one of the most important antioxidant enzymes. A number of investigators have reported that SOD is altered in depression, but the results are inconsistent. The majority of studies have found that SOD activity is increased in depression [186–190], but opposite results have also been reported [191–193]. A meta-analysis by Jimenes-Fernandes et al. [185] revealed higher SOD levels in patients with MDD in comparison to healthy controls. Increased SOD in depression probably reflects activated defense against ROS and RNS [168]. Plausible explanations for inconsistencies in the published results are severity, stage and duration of illness as well as a possible biphasic response in ROS production [177,191,194]. It is worth noting that greater reductions in SOD activity were observed in recurrent depression [191].

As for the effect of antidepressant treatment on SOD activity, the results are also inconsistent [23]. This may be due to methodological differences such as different drugs used, heterogeneity of the disease, differences in severity and the number of episodes.

4.5. Other Enzymes

Catalase (CAT) and myeloperoxidase (MPO) are antioxidant enzymes, the activity of which increases during depressive episodes [176,195,196]. An increase in antioxidant enzyme activity during acute depressive episode is possibly due to the activation of compensatory mechanisms in response to increased oxidative stress. Antioxidant enzyme activity normalizes following treatment and therefore they could serve as state markers of depression [181]. Nevertheless, in a meta-analysis performed by Jimenez-Fernandez [185], differences in CAT appeared nonsignificant. Lower paraoxonase (PON) activity, a potent antioxidant linked to HDL activity, was found in the sera of patients with MDD [164]. At the same time, significantly increased activity of pro-oxidative xanthine oxidase was observed in patients with MDD [192].

4.6. Lipid Peroxidation Markers

Lipid peroxidation is caused by the action of ROS/RNS on lipids (e.g., cell membrane lipids). Early-stage lipid peroxidation is reflected by higher lipid hydroperoxide levels, whereas late-stage lipid peroxidation is characterized by an increase in malonylo-dialdehyde (MDA), 4-hydroxy-2-nonenal (4-HNE) and F2-isoprostanes levels [197]. Lipid peroxidation is more pronounced in patients with MDD than in controls [181]. In a meta-analysis by Mazereeuw et al. [198], lipid peroxidation was correlated with depression severity. Peripheral lipid peroxidation markers are good surrogate markers for their central concentrations [199].

4.6.1. F2-Isoprostanes

F2-isoprostanes are products of arachidonic acid peroxidation. They are chemically stable, which makes them good and reliable markers of lipid peroxidation [200,201]. Higher concentrations of F2-isoprostanes have been found in urine [202,203] and blood [204,205] of patients with MDD. Meta-analyses confirmed that F2-isprostanes are upregulated in MDD [164,206] and correlated with severity of depression. Lindqvist et al. [115] demonstrated that higher baseline levels of F2-isoprostanes correlate with poorer treatment outcomes.

4.6.2. Malonylo-Dialdehyde, Thiobarbituric Acid Reactive Substances

MDA upregulation in MDD is widely documented [164,185–189,194]. Interestingly, MDA concentrations are higher in subsequent depressive episodes compared to the first episode of MDD [191,193].

Thiobarbituric acid reactive substances (TBARS) are a measure of oxidative tissue damage which could be used instead of MDA, albeit with low sensitivity and specificity. Elevated TBARS levels are reported to be trait markers of depression [125].

4.6.3. Lipid Peroxidation Markers Following Treatment

According to a meta-analysis, antidepressant treatment leads to a decrease in lipid peroxidation markers [198]. The majority of studies and meta-analyses report decreased MDA concentrations following antidepressant treatment [164,185,187,188] which correlates with clinical improvement [186,194]. However, some studies did not establish a direct association between lipid peroxidation marker concentrations and clinical remission during antidepressant treatment, suggesting that these two parameters may be causally related but desynchronized [55,207]. By contrast, Chung et al. [202] found that F2-isoprostane levels increase after antidepressant treatment and this increase is correlated with alleviation of depressive symptoms.

The exact mechanism of how antidepressant treatment impacts inflammatory processes and oxidative stress is not fully understood. Following recovery, depressive patients often start looking after themselves, live healthier lives, eat more nutritious food, and exercise, and it cannot be ruled out that the observed reductions in oxidative stress and inflammatory parameters are epiphenomena of such lifestyle changes [23].

4.7. Neoepitopes

Oxidative and nitrosative stress causes brain, muscle and nerve injury, which eventually leads to the formation of new epitopes (neo-epitopes) that can induce immunological IgM/IgG response against them [208]. Antibodies against neo-epitopes have been detected in depression [177,209,210]. Higher concentrations of IgM against conjugated oleic, palmitic, myristic and azelaic acids, MDA, phosphatidyl inositol (Pi), NO-modified neo-epitopes, such as NO-tyrosine, NO-arginine, NO-TRP, NO-bovine serum antigen as well as IgG against oxidized low-density lipoprotein (oxLDL) have been described [177,209–212]. Interestingly, elevated levels of oxLDL antibodies are also found in cardiovascular diseases (e.g., atherosclerosis), autoimmunological diseases (e.g., lupus) and in diabetes [177], which could partly explain the high comorbidity between these diseases and could suggest their common pathophysiological background.

4.8. Nucleic Acids Damage

Oxidative stress can also cause DNA damage, which, combined with less efficient DNA repair, leads to increased DNA damage in depressed patients and contributes to mitochondrial dysfunction [9]. 8-OHdG is a reliable marker of DNA damage [200,213]. Increased blood and urine levels of 8-OHdG have been found in depressive patients [115,213–215]. A meta-analysis confirmed the upregulation of 8-OHdG in patients with MDD [206]. Elevated 8-OHdG levels correlate with MDD severity [215, 216], and are higher in recurrent depression as compared to the first episode of the disease [215]. Enhanced 8-OHdG levels have been reported after SSRI treatment, but only in non-responders [115]. Jorgensen et al. [216] found that the RNA analogue of 8-OHdG—8-oxo-Gua—was elevated in the urine of depressive patients. However, they also reported significant increases in 8-oxo-Gua after ECT.

4.9. Glutathione

Findings relating to glutathione in depression are inconsistent. Its levels are lower in patients with MDD in most studies [181,190]. However, glutathione peroxidase (GPx) activity is reported to be increased [186], decreased [190,193] or not altered [187] in depressed patients compared to healthy

control groups. Differences in GPx between depressed patients and healthy controls are nonsignificant according to the findings of a meta-analysis [185].

Plasma glutathione peroxidase activity decreased after antidepressant treatment [186]. Interestingly, an antioxidant agent—N-acetylo-cysteine (N-ACC)—could be useful in the treatment of depression [217,218]. N-ACC mimics GPx activity, which could exert an antidepressant effect [168]. The effectiveness of N-ACC may suggest the contribution of oxidative stress to treatment resistance in depression.

4.10. Uric Acid

Decreased levels of antioxidant uric acid have been reported in MDD in a meta-analysis. The concentrations of uric acid increased after antidepressant treatment [164,185].

4.11. Albumin

Hypoalbuminemia has been described in depression [13,164]. An increase in albumin levels following antidepressant therapy has been confirmed in a meta-analysis [164].

4.12. Coenzyme Q

Decreased levels of antioxidant coenzyme Q (CoQ) which induce impaired antioxidant protection and enhanced production of damaging TNF-α have been reported in depression [219]. Decreased CoQ is associated with chronic fatigue syndrome which is closely related to fatigue and somatic (F&S) symptoms of depression, described by Maes [219].

4.13. Zinc

Zinc levels have been reported to be reduced in depression and to increase after antidepressant therapy in meta-analyses [164,185]. The role of zinc in MDD was reviewed by Styczeń et al. [220]. Decreased concentrations of CoQ and zinc are both hallmarks of TRD [173].

4.14. Vitamin C

Vitamin C is known to have antioxidant properties. Antidepressant therapy increases vitamin C levels in patients with MDD [164]. That is why, vitamin C could potentially be considered as treatment-response biomarker of depression.

5. Neuroendocrine Findings in Depression

5.1. The Role of the Hypothalamus–Pituitary–Adrenal Axis

The influence of stress and the hypothalamus–pituitary–adrenals axis (HPA axis) activity on the pathophysiology of depression has been extensively studied since the 1960s. Stress axis disturbances are present in approximately 50%–70% of depressive patients [15]. Elevated concentrations of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH) and decreased dehydroepiandrosterone (DHEA) levels have been reported in MDD.

5.1.1. Cortisol

Chronic stress cause hypercortisolemia. Elevated cortisol levels have been repeatedly reported in depression [221,222]. Cortisol can be measured in different specimens such as blood, urine, saliva and even hair (Figure 4). By way of illustration, elevated cortisol in saliva after waking can serve as a biomarker for depression in adolescents [223] and an elevated cortisol concentration in hair could be a new measure of chronic stress exposure. An enhanced hair cortisol concentration could help differentiate between depression and other psychiatric disorders (Herane et al., 2015). Hypercortisolemia has been linked to severe cases of MDD, melancholic and psychotic depressive subtypes [21,224], psychogenic

depression [225] and depression with ruminations [226]. A higher cortisol concentration predicts poorer outcomes of both psychological [227] and pharmacological treatment [228], and an elevated cortisol/DHEA ratio has been described as a marker for TRD, persisting after remission [229].
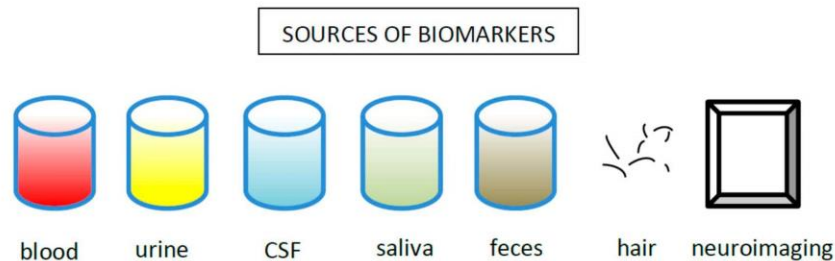

Figure 4. Sources of biological markers used in depression.

On the other hand, decreased cortisol concentrations are characteristics of atypical depression [224] and could be useful in differentiating between melancholic and atypical subtypes of the disease [230]. Hypo-cortisolism could also partly explain higher reward dependence and rejection sensitivity in patients with atypical depression [21].

Hypercortisolemia exerts a detrimental effect on the limbic system (particularly on CA3 neurons in the hippocampus). Under physiological conditions, the hippocampus and amygdala participate in feedback inhibition of the HPA axis through glucocorticoid receptors which are present in hippocampus cells [26]. The hippocampus damaged by elevated levels of cortisol is less efficient in HPA inhibition, which further enhances HPA hyperactivity, creating a vicious circle [11,221]. Cortisol-mediated decreased hippocampal cells proliferation and reduced neurogenesis lead to atrophic changes and volume reductions of the hippocampus which are observed in depressive patients [224,231–233].

It is not clear if the dysregulated HPA axis actually causes depression or if some other feature of depression is responsible for HPA malfunction. However, some depressive symptoms are undoubtedly produced by the dysfunctional HPA axis [11].

5.1.2. Dexamethasone Suppression Test

In early studies, the dexamethasone suppression test (DST) was reported to identify melancholic depression [234,235]. However, later studies dampened enthusiasm and revealed its insufficient sensitivity [236] and specificity [237] to be a diagnostic biomarker. Nevertheless, DST could still potentially be used as a subtyping biomarker or state-dependent biomarker (as conversion from non-suppression to suppression in DST is correlated with a clinical response to antidepressant therapy) [238]. Moreover, an excessive cortisol response to the dexamethasone-suppressed CRH test (Dex-CRH test) after antidepressant treatment could predict a higher risk of recurrence [239].

5.1.3. Corticotropin-Releasing Factor

The levels of corticotropin-releasing factor (CRF) are higher in some depressive patients [240]. However, in a quantitative summary, no significant increases in CRF in depressive patients compared to healthy controls were observed [222]. Interestingly, there are significant parallels between stress response, severe depression and central administration of CRF [240], which supports the involvement of CRF in the pathophysiology of depression. Higher levels of CRF mRNA and CRF have also been observed in the brain of depressive patients who committed suicide [241,242].

5.1.4. Adrenocorticotropic Hormone

Elevated ACTH levels have been reported in patients with MDD [222]. Additionally, higher baseline ACTH levels in patients with BclI polymorphism in the glucocorticoid receptor gene predicted a poorer response to SSRI [243].

5.2. Thyroid Hormones

A significantly higher prevalence of thyroid dysfunctions is observed in patients with MDD/BPD [244]. Hypothyroidism may play a role in depressed mood [245], but the use of thyroid hormones as potential markers requires further investigation [180].

5.3. Nocturnal Melatonin Secretion

Melatonin, a derivate of serotonin, is a major hormone regulating the sleep-wake cycle. Diurnal melatonin secretion changes throughout the day. Nocturnal melatonin secretion has been reported to be higher [246] or lower [247] in patients with MDD in comparison to healthy controls. The phase angle between the cortisol acro-phase and dim-light melatonin onset has been proposed as a potential marker to distinguish individuals with MDD from healthy controls [248].

Interestingly, central administration of IL-1β decreased nocturnal melatonin secretion in sheep, which could suggest a link between inflammation, depression and sleep disturbances [249].

6. Growth Factor Findings in Depression

Growth factors are very promising markers for depression. Brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF) and VGF nerve growth factor are all involved in the pathophysiology of depression and are modulated by antidepressants. Moreover, they are present in the brain and in the periphery, which makes them suitable as biomarkers for psychiatric disorders [250–253]. Chronic stress impacts on the concentrations of growth factors. Reduced neurotrophic support inhibits neurogenesis (notably in the hippocampus and neocortex), which is likely to cause depression [11,254].

6.1. Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is by far the most extensively investigated growth factor in psychiatric research. Plasma BDNF can reflect central BDNF [255], which makes it a reliable peripheral biomarker of brain processes.

6.1.1. Physiological Role

Under physiological conditions, BDNF plays a critical role in cellular resilience and neuroplasticity, enhances long-term potentiation (LTP) [11] and modulates the monoamine system. It also activates intracellular pathways such as mitogen-activated protein kinase/extracellular signal-regulated kinases (MAPK/ERK) pathways. Diminished MAPK/ERK pathway activity together with decreased cyclic adenosine monophosphate (cAMP) levels are known to be involved in the pathophysiology of depression [256].

6.1.2. BDNF in Depression

Baseline BDNF levels are decreased in patients with MDD compared to healthy controls and the magnitude of a decrease in BDNF is negatively correlated with depression severity, as confirmed by meta-analyses [35,40,257–260]. Smoking [261] and diabetes [262] are accompanied by a decreased BDNF concentration in blood and both are independent risk factors for depression. Lower concentrations of peripheral BDNF mRNA in patients with MDD have also been found [94,263]. However, differences in BDNF mRNA expression were not related to symptom severity [263]. Two micro-RNA molecules—miR-132 and miR-182—regulate the expression of BDNF. Serum levels of these micro

RNAs were significantly higher in unmedicated patients with MDD versus healthy controls, which was correlated with a decrease in serum BDNF levels [264].

Alterations in BDNF are not specific to MDD and can serve as a state biomarker in MDD, BPD and schizophrenia [265]. BDNF mediates the detrimental effect of HPA axis abnormalities on the brain [266]. Peripheral BDNF is neither a sufficient measure of MDD severity [260], nor does it discriminate between MB, BPD and schizophrenia. However, BDNF differentiates between mood states in BPD [267], and between acute and remitted states in MDD [265]. BDNF levels are also decreased in Alzheimer's disease, which could support the hypothesis that depression belongs to the spectrum of neurodegenerative diseases [268].

The BDNF gene is induced by the cAMP response element binding protein (CREB) which binds to DNA sequences called CRE (cAMP response elements) and regulates BDNF gene transcription. The functions of CREB and BDNF are region-specific and vastly different in different brain parts. In the hippocampus they have an antidepressant effect, whereas in the ventral tegmental area and nucleus accumbens, BDNF produces a depression-like effect [11,224].

6.1.3. BDNF as a Predictive Biomarker

Serum BDNF may act as a marker of predisposition to depression [269,270]. Decreased serum BDNF with normal cortisol levels may represent a relevant biomarker for individuals more likely to develop depression [180].

6.1.4. Changes in BDNF Following Treatment

Decreased BDNF concentrations in depression normalize in response to pharmacological treatment [35,260,271–273] and ECT [274]. An increase in serum BDNF in response to antidepressant treatment successfully differentiates responders from non-responders [275]. However, antidepressant treatment causes an increase in BDNF levels even in the absence of clinical remission [260]. Therefore, BDNF has potential to be both a trait and a state biomarker [36].

The most widely used antidepressant drugs—SSRIs—produce an immediate increase in monoamine transmission but their mood-enhancing properties appear after weeks of treatment (Krishnan and Nestler, 2008a). The effect of antidepressant drugs is presumably mediated via changes in downstream events such as alterations in gene expression [276]. Apart from normalizing monoamine levels, antidepressants activate CREB which upregulates the expression of growth factors: BDNF, VEGF, VGF in the hippocampus. Growth factors promote hippocampal function, protect vulnerable neurons and, over time, lead to neurogenesis which eventually produces an antidepressant effect [224,232,277].

6.2. Insulin-Like Growth Factor-1, Growth Hormone

According to a recent umbrella meta-analysis, insulin-like growth factor-1 (IGF-1) is another growth factor which is significantly elevated in depression [40]. However, alterations in IGF-1 are not specific to MDD since IGF-1 is also enhanced in the manic phase of BPD [278]. There are promising preclinical studies in which the central or peripheral administration of IGF-1 increases hippocampal neurogenesis and decreases depressive symptomatology [279–282].

Decreased growth hormone (GH) levels have also been reported in patients with MDD [148,154].

6.3. Vascular Endothelial Growth Factor

VEGF is the main growth factor responsible for angiogenesis. Providing vascularization and blood support, it enhances neuron proliferation in the hippocampus [283]. VEGF may play a role in the pathogenesis of depression [250], although its exact role is not yet known. Data relating to VEGF levels in the blood of patients with MDD are not uniform, which may be due to the heterogeneity of depression and may reflect differences between its subtypes. However, the majority of studies indicate that VEGF is elevated in depression and normalizes under antidepressant treatment [284–286].

Higher VEGF concentrations have been observed in remitted MDD and in patients with a family history of depression [180].

6.4. Fibroblast Growth Factor-2

Significantly elevated FGF-2 levels have been reported in depressive patients [40,287]. Together with BDNF, FGF-2 is a second important growth factor marker in depression. Preclinical observations suggest that FGF-2 could mediate antidepressant effects [288]. Some connective tissue growth factors are co-activated in the inflammatory state and therefore their increase in depression may be the result of neuroinflammation [289].

6.5. VGF Nerve Growth Factor

VGF nerve growth factor concentrations have been found to be altered in depression, normalizing after antidepressant therapy, but only in clinical responders [94,290]. Additionally, it has potential as a treatment-response biomarker.

6.6. Nerve Growth Factor, Glial Cell Line Derived Neurotrophic Factor

The levels of nerve growth factor (NGF) and glial cell line derived neurotrophic factor (GDNF) are decreased in depression and the magnitude of dysregulation of these factors correlates with depressive symptoms severity. However, they do not change in response to antidepressant treatment [260].

7. Neurotransmitter Findings in Depression

Alterations in brain neurotransmitter levels—serotonin (5-HT), dopamine (DA) and norepinephrine (NA)—are considered a direct cause of depression. Even if this hypothesis is now thought to explain the pathogenesis of depression only partly, monoamine alterations in depression have been proven and the vast majority of antidepressant drugs currently used target monoamine systems. A search for monoamine-derived markers of depression is hindered by the fact that it is rarely possible to measure monoamine concentrations themselves. Scientists have to rely on peripheral monoamine metabolites, which do not necessarily reflect monoamine levels in the brain. Cerebrospinal fluid (CSF) content appears to reflect brain metabolites more accurately, but its acquisition is difficult and invasive. New imaging technologies are an invaluable tool for measuring brain neurotransmitters. However, a precise description of imaging biomarkers is beyond the scope of this review.

7.1. Serotonin

Serotonin is commonly known as a 'happiness hormone'. Surprisingly, a decrease in 5-HT in the brain, measured by concentrations of serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in CSF, have not been found characteristic of depression itself, but rather of impulsivity [291], suicidality and a tendency to violence [292]. Serotonin exerts its action via the 5-HT1A receptor which has been reported to play a role in both prognosis and diagnosis of depression [293] as reduced 5-HT1A receptor binding is associated with depression [294]. Additionally, increased autoimmune responses to 5-HT were found to correlate with successive depressive episodes [295].

5-HT2A receptor can be found at blood platelets. The density of platelet 5-HT2A receptor tends to increase in patients with depression. However, it has been found to correlate more closely with suicidality than depression per se [296]. Increased 5-HT2A receptor density could potentially serve as a marker of suicide risk (state marker of depression).

7.2. Dopamine

Decreased dopamine levels in the striatum and cortex have been reported in depression [180]. Abnormalities in dopaminergic transmission have also been found in the nucleus accumbens and ventral tegmental, which are core parts of the brain reward circuit [297].

7.3. Noradrenaline

Noradrenaline is of major importance in MDD [298] and is perhaps the most promising source of neurotransmitter markers. There is a correlation between urine NA levels, and depression and anxiety symptoms [299]. Low urinary excretion of NA metabolite—3-methoxy-4-hydroxyphenylglycol (MHPG)—predicts a positive response to NA-selective drugs (e.g., imipramine) [300]. NA concentration in urine is a promising biomarker for guiding treatment selection and predicting its efficacy. MHPG together with a DA metabolite—homo-vanillic acid (HVA)—increase in line with a decrease in depressive symptoms. Lower levels of these metabolites predict a better response to SSRI.

7.4. Monoamine Oxidase Activity

Monoamine oxidases (MAO) are a family of monoamine-catabolizing enzymes. MAO-B is the most important of them. A reduction in MAO-B activity could be an early marker of response to antidepressant treatment [301].

7.5. Glutamate, GABA

Apart from the contribution of monoamines to the pathophysiology of MDD, dysfunction of glutamatergic transmission is also involved in the disorder [302]. Glutamate is a major excitatory neurotransmitter in the brain. Its upregulation causes excessive extra-synaptic N-methyl-D-aspartate receptor (NMDAR) activation leading to the influx of calcium ions (Ca^{2+}) into neurons and accumulation of ROS in the neuron body [303]. As a consequence, it enhances the production of NO, which contributes to the occurrence of MDD [179,304].

Depression is associated with cortical hyper-glutamatergia and increased peripheral glutamate concentration [40,305,306]. Increased glutamate in MDD is closely related to decreased 5-HT and NA. Elevated levels of glutamate cause excitotoxicity, which contributes to the development of depression [180].

Gamma-aminobutyric acid (GABA) is known to be a major inhibitory neurotransmitter in the brain. Changes in glutamate and GABA increase the risk of oxidative stress and cell death [307]. Increased GABA enables the kindling action of glutamate and excessive glutamatergic activity leads to synaptic remodeling and neurodegeneration [180]. According to certain studies, an imbalance in the glutamate/GABA ratio could be a feature of depression [308]. GABA itself has been reported to be a trait biomarker for depression [309,310]. However, later studies revealed that it increases in response to antidepressant treatment [311].

8. Metabolic Findings in Depression, Lipidomics

To date, most studies of depression have focused on proteins. Phospholipids, however, account for 60% of dry mass of the brain [312] and play important biological roles, and hence particular emphasis should be placed on them in psychiatric research [313]. The lipid profile is disturbed in depression, but the exact character of the changes has not been fully elucidated [314]. Many lipid species have been linked to depression: glycerolipids, glycerophospholipids, sphingolipids, and triglycerides [315], and therefore it could be more effective to assess the entire lipid profile rather than particular types of lipid molecules separately. A higher BMI, which is frequently due to an excess of adipose tissue, is associated with a heightened risk of depression [316] and individuals suffering from depression are more likely to develop obesity [317]. It remains an open question as to whether lipid disturbances are a cause or consequence of depression. Among metabolic markers, polyunsaturated fatty acid (PUFA) disturbances and total cholesterol alterations appear to have the greatest potential as markers for depression.

8.1. Polyunsaturated Fatty Acids

A large number of lipidomic depression studies have investigated PUFAs. There are two main types of PUFA: omega-3 and omega-6. Both of them are present in the brain, but each one has a different mode of action. While omega-6-PUFAs (e.g., arachidonic acid) are pro-inflammatory, omega-3-PUFAs (e.g., eicosapentaenoic acid, EPA) possess anti-inflammatory properties [312,318]. Omega-3 acids increase the fluidity of cell membranes and exert a positive impact on neuronal development and neuronal transmission. In depression, blood levels of PUFAs are abnormal, with decreased eicosapentaenoic acid and other omega-3-PUFAs, and increased omega-6-PUFAs, including arachidonic acid concentrations, as reported in a number of studies [312,319–321]. Common depression comorbidities, such as cardiovascular diseases (CVD), diabetes, immunological and inflammatory activation, osteoporosis and cancer are also correlated with decreased omega-3-PUFAs [312]. A more significant decrease in omega-3-PUFAs is correlated with more severe depression [321]. Maes et al. [322] reported an elevated omega6/omega3 ratio in MDD. Elevated HDL and omega-3-PUFAs may have a protective effect on depression-mediated inflammation. Omega-3 supplementation (particularly EPA) improves treatment outcomes [323].

8.2. Cholesterol

Cholesterol also plays a role in depression. It does not cross the blood-brain barrier, but it is synthetized and recycled locally in the brain, mainly by oligodendrocytes [313]. A recent umbrella meta-analysis demonstrated that a decreased total cholesterol level is a highly suggestive marker for MDD [40,324]. As for cholesterol fractions, patients with MDD present with lower HDL and higher LDL concentrations, and a higher LDL/HDL ratio [164,325], which leads to immunological activation. Lower HDL may predict new-onset MDD in the older population [326].

8.3. Sphingomyelin

Sphingomyelin is a type of lipid found in the myelin sheath surrounding neural cell axons. The sphingomyelin 23:1 to sphingomyelin 16:0 ratio has been found to be inversely related to the severity of depression [327].

8.4. Adipokines

Patients with MDD have altered levels of adipokines [328]. Lower adiponectin levels have been reported solely in atypical depression [151].

8.5. Leptin and Ghrelin

Metabolic peptides—leptin and ghrelin—appear to be altered in depression, revealing a potential link between obesity and mood disturbances. However, the results of available studies are inconsistent—decreased, elevated or unchanged levels of leptin and ghrelin have been reported in depressive patients in comparison to healthy controls [329–333].

9. Proteomic Biomarkers

9.1. Insulin

Depression is frequently associated with impaired glucose tolerance, insulin resistance and diabetes [334–336]. Hyperglycemia contributes to inflammation in the brain which could cause depression.

According to certain studies, higher insulin levels in CSF might be the best biomarker to differentiate between patients with MDD and healthy controls [154].

9.2. p11 Protein

Another protein reported to be altered in depression is p11 protein. It is involved in serotonin signaling. Downregulation of p11 protein in NK cells and monocytes during antidepressant treatment correlates with a subsequent reduction in depression severity [337].

10. Transcriptomic Biomarkers

Transcriptomic biomarkers such as micro-RNA (mi-RNA) and long non-coding RNA (lncRNA) have also been investigated in depression. Pajer et al. [338] found a panel of 11 transcripts which were able to differentiate between the presence or absence of depression in animals and a panel of 18 transcripts common to depression and anxiety. Some of them may be more useful in diagnosing depression and some in predicting response to treatment [338,339]. Bocchio-Chiavetto et al. [340] demonstrated that 28 mi-RNAs are upregulated and 2 mi-RNAs are downregulated following antidepressant therapy.

It is worth noting that the increased expression of mRNA for pro-inflammatory cytokines IL-6, IL-1a, IL-1β, IL-8, IL-10, TNF-α, MIF, INF-γ) has been found in the peripheral blood of depressed patients [94,341–343].

More information on transcriptomic factors related to depression can be found elsewhere [36].

11. Kynurenine Pathway, Tryptophan

Tryptophan (TRP) is an amino-acid which is probably most directly implicated in the etiopathogenesis of depression. Under physiological conditions, it is transformed firstly into serotonin and then into melatonin. Serotonin is thought to regulate mood whereas melatonin is responsible for regulating sleep, both of which are disturbed in depression. Tryptophan depletion reduces 5-HT synthesis. The intensity of depressive symptoms correlates with the level of TRP depletion during antidepressant treatment [344].

Tryptophan is essential for T cell proliferation and cytotoxicity. Depletion of TRP (as is the case in depression) leads to T cell anergy [345] and subsequently to immunosuppression. A meta-analysis performed by Ogawa et al. [346] demonstrated reduced TRP levels in the plasma of patients with MDD. Decreased TRP could be a specific marker for MDD and BPD [180], and may play a central role in the pathophysiology of depression. It has been proven that injection of L-TRP modifies brain serotonin levels in rats [347]. On the other hand, injection of branched-chain amino-acids (valine, leucine, isoleucine), which compete with TRP, causes TRP and 5-HT depletion, and eventually, lowered mood [348]. A decrease in branched chain amino-acids following antidepressant treatment correlates with clinical improvement [349].

Apart from TRP depletion, an alternative pathway of TRP metabolism is activated in depression [350]. Systemic inflammation, with high levels of pro-inflammatory cytokines (e.g., INF-γ, TNF-α) along with elevated cortisol, produces sickness behaviour and facilitates the activation of IDO in the brain [345,351–353]. This enzyme transforms TRP into kynurenine [354] in the so-called TRYCATs pathway (tryptophan catabolites along the IDO pathway). Interestingly, the blockage of IDO reduces depressive symptoms without reducing sickness behaviour [352,353], which suggests that IDO is responsible for transformation from sickness behaviour to inflammation-induced depression. Enhanced activity of IDO has been observed in somatization, after suicide attempts and in adolescents with melancholic depression [23]. Interestingly, IDO also possesses antioxidant properties [355]. It has been demonstrated that alterations in the symptoms of depressed patients are positively correlated with kynurenine and negatively correlated with 5-HT concentrations [143]. The TRYCATs pathway produces kynurenine metabolites: 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA) and quinolinic acid (QA) which are cytotoxic and neurotoxic, affecting neurons and T lymphocytes [345]. QA acts as a NMDAR agonist, thus causing excitotoxicity. Its action could be reversed by ketamine—a NMDAR antagonist—recently described as a rapid-acting antidepressant.

Enhanced levels of TRYCATs correlate with higher psychiatric rating scores in depressive patients [356], which could make them markers of depression severity. It should be noted here that most of the brain kynurenine originates from the periphery [345].

In terms of biochemical markers, the kynurenic pathway provides three highly suggestive markers for depression: decreased kynurenic acid (KYNA), decreased KYNA/3HK ratio and decreased KYNA/QA ratio [40,357]. Myint et al. [358] reported no changes in kynurenine pathway markers after antidepressant treatment.

An interesting distinction regarding the role of different types of glial cells in the kynurenic pathway has been made: KYNA—neuroprotective kynurenine metabolite—originates from astrocytes, while neurotoxic QA is produced only by microglia [359]. However, the exact role of astrocytes and microglia in depression is still to be elucidated.

12. The Role of Glial Cells

Glial cell disturbances contribute to the development of depression. It appears that there is a 'creative balance' between pro-inflammatory microglia, Th1 lymphocytes and M1 macrophages on one side and anti-inflammatory astroglia, Th2 cells, Tregs and M2 macrophages on the other. The former components are responsible for IL-1β, Il-2, IL-6, TNF-α, INF-γ production. The latter cells produce IL-4, IL-5 and IL-10. T cell activation with a Th1 shift is observed in depression [135]. Th1 cells activate IDO in the brain, which leads to neurotoxic QA synthesis. It activates NMDAR, which leads to hyper-glutamatergia and further Th1 activation.

In depression, the balance between glial cells is shifted towards microglial activation. Increased microglial activation and proliferation (MAP) is attributable to MDD, but not to BPD. Antidepressant treatment has been found to inhibit M1 microglia polarization [360]. On the other hand, astroglial loss in depression is reported in the anterior cingulate cortex, prefrontal cortex, amygdala and the white matter. The introduction of an astroglial-toxic agent—L-alpha-aminoadipic acid—provoked depressive symptoms in rats [361]. Glial loss leads to the release of cytokines which dysregulate glutamate metabolism leading to a further increase in cytokine concentrations. This leads to the upregulation of S100 calcium-binding protein B (S100B) and alterations in the blood-brain barrier function, which contributes to neuroinflammation. Elevated serum S100B levels have been observed during acute depressive episodes and mania [362]. Serum S100B has been found to correlate with suicidality in MDD and BPD.

13. Metabolomic Biomarkers

Depression research will undoubtedly take advantage of metabolomics—measuring small molecules (metabolites) in biological samples [363]. Scanning of the patient's entire metabolome (a non-targeted approach) is a reasonable approach to identify new biomarkers and new pathways involved in depression. ELISA and Western-blot tests are then used to validate proposed biomarkers [6]. The metabolomic approach is a rapidly growing field with great potential for producing new biomarkers for depression.

13.1. Diagnostic Biomarkers

Metabolomic profiles are different in depressed individuals in comparison to healthy controls [364]. It has been demonstrated that a combination of plasma TRP, glutamate and cysteine can differentiate depressive patients from healthy controls [365]. Elevated plasma amino acid concentrations differentiated patients with melancholic depression from healthy controls [366]. In patients with MDD and heart failure, higher concentrations of amino-acids glutamate, aspartate and cysteine have been observed along with the dysfunction of fatty acids [367]. Downregulated N-methyl-nicotinamide and hippuric acid, and upregulated azelaic acid have been found in the urine of patients suffering from depression alone [368,369]. Paige et al. [364] found higher levels of lipid metabolites and neurotransmitter metabolites in the blood of elderly patients with MDD (dicarboxylic fatty acids,

glutamate, and aspartate). GABA, citrate, glycerate, 9,12-octadecadienoate and glycerol concentrations were reduced in currently depressed patients [364]. A urinary biomarker panel for diagnosing patients with depression and anxiety was proposed by Chen et al. [370]. The simplified panel consisted of four metabolomic biomarkers: N-methyl-nicotinamide, amino-malonic acid, azelaic acid and hippuric acid. Significant differences in metabolic phenotypes between non-medicated depressed patients and healthy controls were revealed, whereas differences between non-medicated and medicated patients were found to be insignificant This may indicate that treatment of depression has a limited impact on metabolites in urine in the patient population [370].

A recently published systematic review performed by MacDonald et al. [371] analyzed metabolomic biomarkers for depression and BPD. The pathway that was most significantly affected both in MDD and BPD was the alanine, aspartate and glutamate pathway. For MDD and BPD, 10 out of 22 metabolic pathways were common. Those specific to MDD were valine, leucine, isoleucine biosynthesis and cyanoamino-acid metabolism [371]. Valine, leucine and isoleucine (branched-chain amino-acids) are involved in the formation of glutamate, which is a major excitatory neurotransmitter responsible for excitotoxicity [372].

In chromatography/nuclear magnetic resonance/mass spectrometry studies, the concentrations of eight metabolites appear to follow a specific trend (up-or downregulation) in urine, CSF and blood of depressed patients. These are increased glutamate, alanine, citrate, formate and decreased phenylalanine, valine, aminoethanol, and hippurate [371]. Glutamate, glycine and cysteine are required for the formation of glutathione [10]. Decreased GABA and increased lactate have been reported to be specific for MDD (MacDonald et al., 2019). The majority of key metabolites are involved in processes such as mitochondrial energy metabolism, signaling/neurotransmission and neuronal integrity [371].

In most studies using in vivo brain imaging techniques, a decrease in brain N-acetylaspartate (NAA), glutamate, creatine, GABA, GSH and phosphocreatine and an increase in brain choline and lactate have been observed [371]. Increased choline levels are in line with cholinergic hyperactivity and adrenergic hypoactivity, described in depression [373]. Mitochondrial dysfunction (e.g., due to oxidative stress) could cause anaerobic glycolysis which may explain elevated lactate levels in the brain. Aspartate is involved in the synthesis of glutamate and NAA. NAA is ubiquitous in neurons and is considered to be a marker of mitochondrial dysfunction and neuronal integrity [374]. NAA increases after antidepressant treatment, which further supports the neurotrophic effects of antidepressants [375].

Most robust biomarkers identified do not follow a specific up-or downregulation trend. This inconsistency is probably due to several variables which have not been taken into consideration in the review such as depressive subtypes, the patient's age, sex, BMI, hormonal and smoking status [371]. Nevertheless, a diagnostic panel for MDD and BPD consisting of lactate, alanine, glycine, phenylalanine, tyrosine, sorbitol, pyroglutamate, aminoethanol and hippurate, and a panel for MDD alone comprising glutamate, citrate, valine and formate have been proposed [371]. It is worth noting that metabolomic research requires strict observance of the patient's inclusion criteria and methodological procedures since the metabolome is highly variable and significant differences in results may appear.

13.2. Prognostic Biomarkers

Metabolomic markers may also potentially serve as prognostic markers in depression. Baseline levels of TRP, phenylalanine, purine and tocopherol could predict responders vs. non-responders to antidepressant treatment [376].

14. Intracellular Pathways

Intracellular signaling networks and transcription factors are likely to be dysfunctional in depression. The Janus kinases-signal transducer and activator of transcription (JAK-STAT) signaling pathway, glycogen synthase kinase-3 (GSK-3), and nuclear factors NF-κB and NRF-2 modulate inflammatory, O&NS and neuro-progressive pathways which are involved in depression [46]. By way of illustration, the expression of NRF-2 is regulated by oxidative stress and is altered in depression [10,377].

The expression of genes regulated by NRF-2 is upregulated in depression and downregulated after successful therapy [378]. The inhibitory impact of lithium on the GSK-3 pathway produces an anti-inflammatory effect and could partly explain the antidepressant effect of lithium [379].

Decreased adenosine triphosphate (ATP) levels have been found in post-mortem brains (dorsolateral prefrontal cortex) of depressed individuals [380]. Interestingly, ATP administration has been proven to have a fast antidepressant effect in mice [381].

A detailed review of intracellular pathway disturbances in depression is beyond the scope of this review and can be found elsewhere [382].

15. Genetics

Genetic contribution to MDD is around 40%–50% [383]. Several single nucleotide polymorphisms (SNPs) have been linked to depression, mainly those involved in monoaminergic and glutamatergic signaling [6]. Polymorphism in genes encoding the 5-HT transporter, 5-HT2A receptor, BDNF, TRP hydroxylase, SOD and CAT are candidate genes in the pathology of MDD [168,384,385]. Nevertheless, in an extensive Genome-Wide Association Study, no robust and meaningful genomic differences were found between MDD and healthy controls despite the large size of the study group [386]. A probable explanation may be the significant heterogeneity of depression and diverse or even opposite DSM criteria. Hence, a change in the paradigm may be necessary. Novel genomic approaches such as polygenic scores [387] or telomere length [388,389] could be more useful.

SNPs in several genes have been associated with response to antidepressant treatment [390], e.g., Met/Met genotype in the catechol-O-methyltransferase (COMT) gene [391]. However, no study has identified genetic variants that could be associated with treatment outcomes at a genome-wide statistical level [392].

16. Epigenetics

Epigenetic changes consist in modifications of gene expression without changes in the DNA sequence. They are mainly mediated by two processes: DNA methylation and histone modifications. Stress (both physical and psychological) is known to activate epigenetic mechanisms which increase the risk of depression [393]. Early life stress and polymorphism in the serotonin transporter gene facilitate methylation of the promoter region of the CRF gene in rats [394]. Stress during pregnancy leads to a higher risk of depression and anxiety in young adults. It is associated with reduced expression of the BDNF and AcH3K14 genes and increased expression of histone deacetylases in the hippocampus [395]. Elevated levels of methylation of the exon 1 promoter region in the BDNF gene have been found in patients with MDD in comparison to healthy controls [396].

17. Physiological Markers

Among 'physiological markers', alterations in circadian rhythms and electroencephalography (EEG) records have been observed in patients with MDD. Altered circadian rhythms are associated with genetic, environmental and developmental abnormalities preceding the development of MDD [397,398]. Korb et al. [399] reported that clinical response to anti-depressant treatment can be predicted by assessing activity in the rostral anterior cingulate cortex region in EEG.

18. Imipramine Binding

Imipramine was the first effective antidepressant drug in history. The binding of imipramine on the surface of platelets is considered a potential biological feature able to differentiate depressed individuals from healthy controls [400]. While several studies reported conflicting results, a meta-analysis performed by Ellis and Salmond [401] confirmed decreased maximal platelet imipramine binding (Bmax) in depressed patients. Nevertheless, the clinical utility of such a marker is questionable.

19. Treatment-Resistant Depression

A distinct problem in depression is the issue of treatment resistance. Early identification of patients at risk of treatment resistance may be possible with the use of biological markers. TRD has been associated with immune activation (enhanced mitogen-induced lymphocyte response, increased CD4/CD8 T cell ratio, enhanced IL-6 trans-signaling with higher sIL-6R, higher CRP and TNF-α), significantly enhanced oxidative stress (higher TBARS) and attenuated immune regulation (low sTNF-R2) in comparison to non-TRD patients [96,125,402,403]. IL-6, CRP, TNF and sTNF-R2 are associated with a number of failed antidepressant treatment attempts [404]. Risk factors for non-response also include elevated concentrations of circulating IL-1β, TNF-α, MIF and cortisol, dexamethasone non-suppression of cortisol, and decreased concentrations of IL-12, TSH, HDL, S100B, serotonin and noradrenaline [405].

20. Depression Subtypes

20.1. Melancholia

As mentioned above, depression is a heterogeneous disorder. This heterogeneity is an obstacle in biomarker research. In this section we would like to analyze in more detail two major depressive subtypes—melancholic and atypical depression.

The prevalence of typical and atypical depression in the general population is 7.1% and 3.5%, respectively [406]. Melancholic depression is a specifier of typical depression according to DSM-5. Approximately 20%–30% of all MDD cases are classified as melancholic depression [407,408].

The history of the term 'melancholia' is long and goes back to antiquity. Throughout the years, this type of depression has been described as endogenous, psychogenic, evolutionary, non-reactive, anhedonic, 'vital depression type' or depression with psychomotor retardation [407]. Melancholic depression is thought to be the most 'pure' endogenous depression. Even though it is difficult to establish precise boundaries of the term 'melancholia', a few characteristics are repeatedly reported in this subtype of depression. Motivational, appetitive and arousal functions are disturbed in melancholia (anhedonia, psychomotor retardation, hyperarousal, stress sensitivity) [407]. Melancholia is often characterized by greater severity, heritability, chronicity and a history of childhood trauma or abuse and comorbid anxiety [20,366,407,409,410]. Chronic low stress causes melancholic type behaviour in mice [411,412]. Melancholic depression is characterized by more significant psychomotor retardation and attention deficits in comparison to NMD [413]. Melancholic depression is more common in females and in advanced age, and is associated with greater severity and more common occurrence of psychotic features [414]. The strong heritable component in melancholia suggests that there may be an underlying biological dysfunction which could be manifested by certain biological features [366].

Melancholic depression appears to be associated with significant dysregulation of the DA system (e.g., higher frequency in people with Parkinson's disease) [415]. Decreased dopaminergic function leads to psychomotor retardation which could underpin learned helplessness [416].

The presence of melancholic features is considered a risk factor for TRD [417]. In melancholic depression, response to SSRI treatment is poorer in comparison to response to drugs modulating multiple neurotransmitters (e.g., tricyclic antidepressants—TCA). This could be caused by a different circuitry characteristic of melancholia—more dopaminergic and noradrenergic, and not only serotoninergic [407,418,419]. In terms of treatment response, lower baseline plasma S100B protein may predict treatment resistance in patients with melancholic depression [420].

20.1.1. Markers to Differentiate Melancholia from Healthy Controls

A significant number of studies have investigated biological features of melancholic depression. Among physiological markers of melancholia, lower systolic blood pressure, higher heart rate and a lower BMI have been found [230]. Melancholia is characterized by HPA axis hyperactivity, CRH dysfunction, higher plasma cortisol with altered cortisol diurnal variation, higher androstenedione and corticosterone

(dysregulation promoting steroidogenesis in the upstream pathway), higher plasma arginine vasopressin, higher central NA, and basal hypothalamic-pituitary-thyroid ultra-sensitivity [230,366]. More pronounced inflammation or deficits in immune regulation have been reported in melancholic depression in comparison to healthy controls [230]. Upregulation of T cytotoxic CD8+ cells, M1 macrophages and Th1 lymphocytes [49,421] as well as downregulation of NK cells and Tregs have been found characteristic of melancholic depression. Melancholic depression is also characterized by increased IL-6 and sIL-6R (enhanced IL-6 trans-signaling) and decreased IL-1α and TGF-β [125,422].

Metabolomic biosignature differentiates patients with melancholic depression from healthy controls. Most metabolites related to lipids and metabolites related to stress hormone signaling are elevated in depression with melancholic features. One study demonstrated different levels of cystine, dodecanal, isoleucine, methionine, leucine, normetanephrine, and phenylalanine in melancholia [366]. Another study reported lower aspartic acid, glycine, GABA and higher NO levels in melancholic depression in comparison to healthy controls [423].

20.1.2. Markers to Differentiate Melancholia from Atypical Depression

Since the performance of the pioneering research by Carroll et al. [235] in 1981, attempts have been made to differentiate two major depressive subtypes—melancholic and atypical—based on the biological profile. HPA hyperactivation and sustained cortisol elevation have repeatedly been indicated as distinct features of melancholic depression which can differentiate it from atypical depression [230,424,425]. Melancholic depression is characterized by a lower absolute monocyte count, increased haptoglobin, IL-6 and CRP, enhanced expression of T cell activation markers, and increased resistance of sIL-2R and IL-1β production in response to dexamethasone administration as compared to non-melancholic depression [426–431]. Higher triglycerides and fatty acids have been observed in the melancholic subtype [366]. Studies suggest that the angiotensin-converting enzyme (ACE) could be decreased in melancholic depression (vs. atypical, vs. healthy controls) [151,432], although published results are inconsistent.

Liu found decreased histamine and decreased arachidonic acid in melancholic depression [366]. The findings are in line with previous studies indicating that melancholic depression is characterized by immune repression in contrast to atypical depression which presents with inflammatory activation [222,424].

Among 'physiological' markers, differences in EEG patterns have been reported between melancholic and atypical depression [433].

20.2. Atypical Depression

Atypical depression differs more from healthy controls than melancholic depression. In a study by Lamers et al. [151], eight out of nine markers overlapped when the authors compared atypical depression with healthy controls and with melancholic depression. No marker reached statistical significance which would allow for differentiating between melancholic depression and healthy controls. The study demonstrated that in atypical depression the following molecules were altered as compared to melancholic depression: higher leptin, FABPa, complement C3, insulin, B2-microglobulin, ACE, and lower insulin-like growth factor-binding protein 1 and 2 (IGFBP1, IGFBP2) and mesothelin. When correcting for BMI, the effect remained significant only for IGFBP1, ACE and B2-microglobulin (the mediating effect of BMI) [151]. The results are not entirely consistent—enhanced leptin was also found in melancholic, but not atypical depression in a POWER (Premenopausal, Osteoporosis, Women, Alendronate, Depression) study [434].

In the majority of studies, atypical depression presents with a more disturbed metabolic profile. Atypical features correlate with a higher BMI, triglycerides and waist circumference, and lower HDL and obesity, which could partly explain elevations in IL-6, CRP, TNF-α, and IL-1β since adipose tissue enhances the production of pro-inflammatory agents [435]. However, metabolic disturbances cannot fully explain the pro-inflammatory shift characteristic of atypical depression [230].

Although some similarities were found between melancholic and atypical depression (e.g., televated IL-6 and CRP concentrations) in a study by Lamers et al. [230], the authors suggest that inflammation per se is characteristic of atypical depression only, while melancholic depression is even thought to present an anti-inflammatory profile. Enhanced inflammation reported in the melancholic subtype in certain studies (e.g., elevated CRP, IL-6, TNF-α) could reflect the characteristics of the study cohort (e.g., patients with more severe symptoms of depression, inpatient). Decreased IL-4 and increased IL-2 have been reported in atypical as compared to melancholic depression [421].

21. Discussion

21.1. The Need for Markers

Psychiatric disorders, including depression, are still not completely understood. Knowledge regarding the etiopathogenesis of depression remains rudimentary. However, thanks to the implementation of new diagnostic techniques and technologies, particularly the 'omics' modalities, new evidence is emerging and our understanding of the complex nature of depression is becoming more profound. At present, depression is regarded as a disorder of communication between neurons, glia and endothelial cells, which is dependent on different systemic factors, including inflammation and oxidative stress [345]. However, this definition is probably incomplete. Biological markers constitute an invaluable aid in finding potential new patho-mechanisms involved in the pathogenesis of depression. Another important issue is a high level of treatment resistance in depression which occurs in more than one third of all MDD cases. Biological markers could help stratify patients into more homogenous subgroups and subtypes, such as melancholic and atypical depression, identify patients at risk of TRD or suicide and elucidate causes and mechanisms underlying these states, such as increased inflammation or pronounced oxidative stress. Biomarker levels can help assess the severity of depression, predict outcomes or guide adequate treatment selection. Lastly, by revealing underlying biological processes, biomarkers may help discover new drug targets and reduce the global depression burden.

21.2. Biomarkers That Have Potential

The selection of the most accurate biomarkers for depression is not an easy task. Research into depression markers has intensified in recent years, revealing a plethora of substances, gene polymorphisms, metabolites and other indicators of depression. Multiple meta-analyses present conflicting results, which may be due to a vast number of small, marginally significant studies, methodological differences between studies, depression comorbidities and the high heterogeneity of depression itself. Nevertheless, inflammatory biomarkers, biomarkers related to oxidative stress, HPA changes, growth factors and kynurenine pathway markers are repeatedly reported in depression studies and have promise to be reliable indicators of depression. The most recent and comprehensive, to date, umbrella meta-analysis by Carvalho et al. [40] demonstrates that depression is associated with increased CRP, IL-6, TNF-α, sIL-2R, IGF-1, FGF-2, glutamate and lipid peroxidation markers, and decreased BDNF, total cholesterol, KYNA, KYNA/3HK and KYNA/QA.

21.3. Looking for Biosignature

No individual marker for MDD has displayed sufficient specificity and sensitivity to be a diagnostic biomarker [436]. Absolute changes in HDRS—the most popular scale to measure depression intensity—are not significantly correlated with alterations in the levels of any particular biomarkers [115]. One of the biggest challenges (and opportunities) of current depression biomarker research is the inevitable and indispensable shift in the paradigm—from studies focused on one or two specific biomarkers (proteins, mutations, etc.) to a far more holistic approach, considering multiple biomarkers of different classes (i.e., a biosignature) [437] and interactions between them (interactome). It may also be the case that questionnaires used for the clinical assessment of depression are not best correlated

with biomarker levels. Perhaps a more holistic approach to the patient's state, including quality of life or everyday functioning, is needed to increase biomarker accuracy [438]. A possible lack of a link between various depression scales and depressive markers may also be due to high levels of comorbid anxiety in depressive patients since anxiety substantially impacts on the stress axis and hormones.

21.4. Issues

Biomarker research in psychiatry is particularly difficult due to a number of issues highlighted below.

21.4.1. Lack of Specificity

Mental diseases have no sharp boundaries and there is a considerable overlap of symptoms between psychiatric entities. In addition, they could be perceived as spectrum disorders [439,440] and psychiatric biomarkers may have a transdiagnostic nature [441].

To address this issue, the Research Domain Criteria Initiative (RDoC) was launched by the National Institute of Mental Health. This postulates a totally new approach to the classification of mental disorders and seeks to connect observed behavioral dimensions with neurobiological systems [442]. It is designed in the form of a matrix concentrating on the assessment of different spheres of mental functioning affected by mental disorders (such as negative and positive valence systems, cognitive system, system for social processes and arousal/regulatory system) at different levels of analysis (genetic, molecular, cellular, neuroanatomical, behavioral, etc.) [33]. This approach goes across existing diagnostic entities, attempting not to replace the DSM-5 but rather to supplement it in a more biological, evidence-based way.

21.4.2. Poor Understanding of the Biology of Depression

Another issue hindering depression research is a lack of broader understanding of its etiopathogenesis. This process has accelerated several times as a result of frequently accidental, discoveries of new antidepressant drugs. Studying the mechanism of action of these drugs eventually led scientists to the construction of new hypotheses of depression. That was the case with, inter alia, imipramine, initially designed as an anti-tuberculosis drug, which unraveled the monoamine mechanism of depression, and ketamine, an NMDAR antagonist, which underpinned the importance of NMDAR activation in the development of depression. However, our knowledge regarding the pathogenesis of depression is still rudimentary. Therefore, when it comes to studies of biomarkers, they frequently only correlate depression with altered levels of a few molecules, without providing a comprehensive explanation of the origin of the observed changes. Some studies ignore the fact that markers are interrelated in a complex, difficult-to-model network (e.g., some could be epiphenomena of others) [438]. Besides, the exact role of markers in healthy individuals and in depressive patients remains largely unknown.

To better understand depression, there is a need for reliable animal models. On the other hand, to build such models, a more comprehensive understanding of the pathophysiology of depression is necessary [11].

21.4.3. Weak Studies

Recent technological advances have contributed to the intensification of research efforts in the field of biomarker discovery, particularly thanks to the expansion of 'omics' technologies which have revealed hundreds of putative biomarkers—gene polymorphisms, proteins and metabolites, whose presence (or altered levels—up or downregulation) could indicate depression. However, the published results are inconsistent and most markers lack robustness and validation and cannot be applied directly to clinical practice, which causes a 'translational gap' [6,40]. This is due to issues including a lack of clear definition of psychiatric illnesses, biomarker variability in individuals, widespread diffusion of small, underpowered studies characterized by 'significance chasing' and small effect size, 'approximate replications' of these studies which neither confirm decisively nor

reject original findings (instead creating a penumbra of new hypotheses), selective publication of 'positive' results, selective reporting of outcomes, and finally, for most studies, focus on comparing 'textbook patients' with perfectly healthy individuals, which limits clinical application of such a biomarker [30,443]. A more profound understanding of individual variables such as patient's age, sex, menstrual cycle, medication use, smoking status, BMI, and time of sample collection are important to ameliorate the accuracy of results [23].

21.4.4. Heterogeneity

A search for biomarkers is also hindered by the heterogeneity of MDD [53,206,444]. A lack of robust, biologically validated, homogenous subgroups is one the greatest obstacles in establishing biomarkers for depression [3]. Making generalized statements about depression is difficult when one considers the plethora of different depressive subtypes described in the literature which are characterized by distinct symptomatologies. It might be worthwhile to use biological differences as a springboard for defining depression subtypes based on biomarker profile analysis utilizing latent class analysis [445].

21.4.5. Brain-Periphery Differences

Peripheral fluids (blood, urine, saliva) are the most obvious sources of biomarkers in various diseases, including MDD. It remains an open question, however, to what degree biochemical changes in peripheral fluids reflect what happens in the brain/CSF. By way of illustration, even if cytokines can cross the blood-brain barrier and elevated levels of cytokines are present both peripherally and centrally in depressed patients [47,53,93,446], the peripheral cytokine profile should not be considered a simple reflection of what is happening in the brain since peripheral cytokines are strongly influenced by several extra-central nervous system (CNS) variables. A poor correlation between blood and brain biomarkers (with some overlaps) was described by Hayashi-Takagi et al. [447]. There are also discrepancies between studies caused by differences in investigated blood samples types (serum, plasma or cellular components).

To sum up, it is very unlikely that a single marker for MDD is established. However, even if the diagnosis of depression continues to be based on clinical signs, biomarkers may be a valuable tool for stratifying particular patients with the disorder, defining subtypes, improving treatment matching, avoiding specific treatment modalities, predicting response, etc. Such biomarker application is already common in other areas of medicine in diseases such as asthma, rheumatoid arthritis or cancer [30].

22. Limitations

The study is not systematic and does not provide quantitative information. The authors did not use strict inclusion and exclusion criteria. Both large and small studies were included. No age and gender bias were considered.

References

1. Smith, K. Mental health: A world of depression. *Nature* **2014**, *515*, 181. [CrossRef] [PubMed]
2. World Health Assembly. *Global Burden of Mental Disorders and the Need for a Comprehensive, Coordinated Response from Health and Social Sectors at the Country Level: Report by The Secretariat*; World Health Organization: Geneva, Switzerland, 2012.
3. Kraus, C.; Kadriu, B.; Lanzenberger, R.; Zarate, C.A.; Kasper, S. Prognosis and improved outcomes in major depression: A review. *Transl. Psychiatry* **2019**, *9*, 127. [CrossRef] [PubMed]
4. Gaynes, B.N.; Warden, D.; Trivedi, M.H.; Wisniewski, S.R.; Fava, M.; Rush, A.J. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr. Serv.* **2009**, *60*, 1439–1445. [CrossRef] [PubMed]
5. Kirsch, I. Antidepressants and the placebo response. *Epidemiol. Psichiatr. Soc.* **2009**, *18*, 318–322. [CrossRef]
6. Gadad, B.S.; Jha, M.K.; Czysz, A.; Furman, J.L.; Mayes, T.L.; Emslie, M.P.; Trivedi, M.H. Peripheral biomarkers of major depression and antidepressant treatment response: Current knowledge and future outlooks. *J. Affect. Disord.* **2018**, *233*, 3–14. [CrossRef]
7. Maes, M. Major depression and activation of the inflammatory response system. *Adv. Exp. Med. Biol.* **1999**, *461*, 25–46. [CrossRef]
8. Maes, M. The cytokine hypothesis of depression: Inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. *Neuro Endocrinol. Lett.* **2008**, *29*, 287–291.
9. Czarny, P.; Wigner, P.; Galecki, P.; Sliwinski, T. The interplay between inflammation, oxidative stress, DNA damage, DNA repair and mitochondrial dysfunction in depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2018**, *80*, 309–321. [CrossRef]
10. Anderson, G.; Maes, M. Oxidative/nitrosative stress and immuno-inflammatory pathways in depression: Treatment implications. *Curr. Pharm. Des.* **2014**, *20*, 3812–3847. [CrossRef]
11. Nestler, E.J.; Barrot, M.; DiLeone, R.J.; Eisch, A.J.; Gold, S.J.; Monteggia, L.M. Neurobiology of depression. *Neuron* **2002**, *34*, 13–25. [CrossRef]
12. Maes, M.; Yirmyia, R.; Noraberg, J.; Brene, S.; Hibbeln, J.; Perini, G.; Kubera, M.; Bob, P.; Lerer, B.; Maj, M. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: Leads for future research and new drug developments in depression. *Metab. Brain Dis.* **2009**, *24*, 27–53. [CrossRef] [PubMed]
13. Maes, M. Evidence for an immune response in major depression: A review and hypothesis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1995**, *19*, 11–38. [CrossRef]
14. Maes, M. A review on the acute phase response in major depression. *Rev. Neurosci.* **1993**, *4*, 407–416. [CrossRef] [PubMed]
15. Gałecki, P.; Talarowska, M. Inflammatory theory of depression. *Psychiatr. Pol.* **2018**, *52*, 437–447. [CrossRef] [PubMed]
16. Maes, M.; Smith, R.; Scharpe, S. The monocyte-T-lymphocyte hypothesis of major depression. *Psychoneuroendocrinology* **1995**, *20*, 111–116. [CrossRef]
17. Patel, A. Review: The role of inflammation in depression. *Psychiatr. Danub.* **2013**, *25* (Suppl. S2), S216–S223.
18. Landgraf, D.; Long, J.; Der-Avakian, A.; Streets, M.; Welsh, D.K. Dissociation of learned helplessness and fear conditioning in mice: A mouse model of depression. *PLoS ONE* **2015**, *10*, e0125892. [CrossRef]
19. Gałecki, P.; Talarowska, M. Neurodevelopmental theory of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2018**, *80*, 267–272. [CrossRef]
20. Lamers, F.; de Jonge, P.; Nolen, W.A.; Smit, J.H.; Zitman, F.G.; Beekman, A.T.F.; Penninx, B.W.J.H. Identifying depressive subtypes in a large cohort study: Results from the Netherlands study of depression and anxiety (NESDA). *J. Clin. Psychiatry* **2010**, *71*, 1582–1589. [CrossRef]
21. Kunugi, H.; Hori, H.; Ogawa, S. Biochemical markers subtyping major depressive disorder: Biomarkers in depression. *Psychiatry Clin. Neurosci.* **2015**, *69*, 597–608. [CrossRef]
22. Osimo, E.F.; Pillinger, T.; Rodriguez, I.M.; Khandaker, G.M.; Pariante, C.M.; Howes, O.D. Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5166 patients and 5083 controls. *Brain Behav. Immun.* **2020**, 901–909. [CrossRef] [PubMed]
23. Lopresti, A.L.; Maker, G.L.; Hood, S.D.; Drummond, P.D. A review of peripheral biomarkers in major depression: The potential of inflammatory and oxidative stress biomarkers. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2014**, *48*, 102–111. [CrossRef] [PubMed]

24. Maes, M. "Functional" or "psychosomatic" symptoms, e.g., a flu-like malaise, aches and pain and fatigue, are major features of major and in particular of melancholic depression. *Neuro Endocrinol. Lett.* **2009**, *30*, 564–573. [PubMed]

25. Goldberg, D. The heterogeneity of "major depression". *World Psychiatry* **2011**, *10*, 226–228. [CrossRef] [PubMed]

26. Lee, S.; Jeong, J.; Kwak, Y.; Park, S.K. Depression research: Where are we now? *Mol. Brain* **2010**, *3*, 8. [CrossRef]

27. Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* **1960**, *23*, 56–62. [CrossRef]

28. Montgomery, S.A.; Asberg, M. A new depression scale designed to be sensitive to change. *Br. J. Psychiatry J. Ment. Sci.* **1979**, *134*, 382–389. [CrossRef]

29. Beck, A.T.; Ward, C.H.; Mendelson, M.; Mock, J.; Erbaugh, J. An inventory for measuring depression. *Arch. Gen. Psychiatry* **1961**, *4*, 561–571. [CrossRef]

30. Kapur, S.; Phillips, A.G.; Insel, T.R. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol. Psychiatry* **2012**, *17*, 1174–1179. [CrossRef]

31. Hirschfeld, R.M. Differential diagnosis of bipolar disorder and major depressive disorder. *J. Affect. Disord.* **2014**, *169* (Suppl. S1), S12–S16. [CrossRef]

32. Cuthbert, B.N.; Insel, T.R. Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Med.* **2013**, *11*, 126. [CrossRef] [PubMed]

33. Insel, T.; Cuthbert, B.; Garvey, M.; Heinssen, R.; Pine, D.S.; Quinn, K.; Sanislow, C.; Wang, P. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* **2010**, *167*, 748–751. [CrossRef] [PubMed]

34. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin. Pharm.* **2001**, *69*, 89–95. [CrossRef]

35. Schmidt, H.D.; Shelton, R.C.; Duman, R.S. Functional biomarkers of depression: Diagnosis, treatment, and pathophysiology. *Neuropsychopharmacology* **2011**, *36*, 2375–2394. [CrossRef] [PubMed]

36. Gururajan, A.; Clarke, G.; Dinan, T.G.; Cryan, J.F. Molecular biomarkers of depression. *Neurosci. Biobehav. Rev.* **2016**, *64*, 101–133. [CrossRef] [PubMed]

37. Ritsner, M.S. (Ed.) *The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes: Volume IV: Molecular Genetic and Genomic Markers*; Springer: Amsterdam, The Netherlands, 2009; ISBN 978-90-481-2297-4.

38. Søreide, K. Receiver-operating characteristic curve analysis in diagnostic, prognostic and predictive biomarker research. *J. Clin. Pathol.* **2009**, *62*, 1–5. [CrossRef] [PubMed]

39. Strawbridge, R.; Young, A.H.; Cleare, A.J. Biomarkers for depression: Recent insights, current challenges and future prospects. *Focus* **2018**, *16*, 194–209. [CrossRef]

40. Carvalho, A.F.; Solmi, M.; Sanches, M.; Machado, M.O.; Stubbs, B.; Ajnakina, O.; Sherman, C.; Sun, Y.R.; Liu, C.S.; Brunoni, A.R.; et al. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. *Transl. Psychiatry* **2020**, *10*, 1–13. [CrossRef]

41. Blume, J.; Douglas, S.D.; Evans, D.L. Immune suppression and immune activation in depression. *Brain Behav. Immun.* **2011**, *25*, 221–229. [CrossRef]

42. Haapakoski, R.; Mathieu, J.; Ebmeier, K.P.; Alenius, H.; Kivimäki, M. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behav. Immun.* **2015**, *49*, 206–215. [CrossRef]

43. Raison, C.L.; Miller, A.H. Is depression an inflammatory disorder? *Curr. Psychiatry Rep.* **2011**, *13*, 467–475. [CrossRef] [PubMed]

44. Del Giudice, M.; Gangestad, S.W. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain Behav. Immun.* **2018**, *70*, 61–75. [CrossRef] [PubMed]

45. Capuron, L.; Su, S.; Miller, A.H.; Bremner, J.D.; Goldberg, J.; Vogt, G.J.; Maisano, C.; Jones, L.; Murrah, N.V.; Vaccarino, V. Depressive symptoms and metabolic syndrome: Is inflammation the underlying link? *Biol. Psychiatry* **2008**, *64*, 896–900. [CrossRef] [PubMed]

46. Maes, M.; Fišar, Z.; Medina, M.; Scapagnini, G.; Nowak, G.; Berk, M. New drug targets in depression: Inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates—Nrf2 activators and GSK-3 inhibitors. *Inflammopharmacology* **2012**, *20*, 127–150. [CrossRef] [PubMed]

47. Howren, M.B.; Lamkin, D.M.; Suls, J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosom. Med.* **2009**, *71*, 171–186. [CrossRef]

48. Raison, C.L.; Capuron, L.; Miller, A.H. Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends Immunol.* **2006**, *27*, 24–31. [CrossRef]
49. Maes, M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 664–675. [CrossRef]
50. Müller, N.; Schwarz, M.J.; Dehning, S.; Douhe, A.; Cerovecki, A.; Goldstein-Müller, B.; Spellmann, I.; Hetzel, G.; Maino, K.; Kleindienst, N.; et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: Results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol. Psychiatry* **2006**, *11*, 680–684. [CrossRef]
51. Leonard, B.E. Inflammation and depression: A causal or coincidental link to the pathophysiology? *Acta Neuropsychiatr.* **2018**, *30*, 1–16. [CrossRef]
52. Krishnadas, R.; Cavanagh, J. Depression: An inflammatory illness? *J. Neurol. Neurosurg. Psychiatry* **2012**, *83*, 495–502. [CrossRef]
53. Dowlati, Y.; Herrmann, N.; Swardfager, W.; Liu, H.; Sham, L.; Reim, E.K.; Lanctôt, K.L. A meta-analysis of cytokines in major depression. *Biol. Psychiatry* **2010**, *67*, 446–457. [CrossRef] [PubMed]
54. Pasco, J.A.; Nicholson, G.C.; Williams, L.J.; Jacka, F.N.; Henry, M.J.; Kotowicz, M.A.; Schneider, H.G.; Leonard, B.E.; Berk, M. Association of high-sensitivity C-reactive protein with de novo major depression. *Br. J. Psychiatry J. Ment. Sci.* **2010**, *197*, 372–377. [CrossRef] [PubMed]
55. Leonard, B.; Maes, M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci. Biobehav. Rev.* **2012**, *36*, 764–785. [CrossRef] [PubMed]
56. Miller, G.E.; Rohleder, N.; Cole, S.W. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. *Psychosom. Med.* **2009**, *71*, 57–62. [CrossRef] [PubMed]
57. Steptoe, A.; Hamer, M.; Chida, Y. The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain Behav. Immun.* **2007**, *21*, 901–912. [CrossRef] [PubMed]
58. Dierker, L.C.; Avenevoli, S.; Stolar, M.; Merikangas, K.R. Smoking and depression: An examination of mechanisms of comorbidity. *Am. J. Psychiatry* **2002**, *159*, 947–953. [CrossRef] [PubMed]
59. Stunkard, A.J.; Faith, M.S.; Allison, K.C. Depression and obesity. *Biol. Psychiatry* **2003**, *54*, 330–337. [CrossRef]
60. Nieman, D.C.; Henson, D.A.; Nehlsen-Cannarella, S.L.; Ekkens, M.; Utter, A.C.; Butterworth, D.E.; Fagoaga, O.R. Influence of obesity on immune function. *J. Am. Diet. Assoc.* **1999**, *99*, 294–299. [CrossRef]
61. Yanbaeva, D.G.; Dentener, M.A.; Creutzberg, E.C.; Wesseling, G.; Wouters, E.F.M. Systemic effects of smoking. *Chest* **2007**, *131*, 1557–1566. [CrossRef]
62. Anisman, H.; Merali, Z. Cytokines, stress and depressive illness: Brain-immune interactions. *Ann. Med.* **2003**, *35*, 2–11. [CrossRef]
63. Catena-Dell'Osso, M.; Rotella, F.; Dell'Osso, A.; Fagiolini, A.; Marazziti, D. Inflammation, serotonin and major depression. *Curr. Drug Targets* **2013**, *14*, 571–577. [CrossRef] [PubMed]
64. Miller, A.H.; Maletic, V.; Raison, C.L. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biol. Psychiatry* **2009**, *65*, 732–741. [CrossRef] [PubMed]
65. Allison, D.J.; Ditor, D.S. The common inflammatory etiology of depression and cognitive impairment: A therapeutic target. *J. Neuroinflammation* **2014**, *11*, 151. [CrossRef] [PubMed]
66. Kinney, D.K.; Tanaka, M. An evolutionary hypothesis of depression and its symptoms, adaptive value, and risk factors. *J. Nerv. Ment. Dis.* **2009**, *197*, 561–567. [CrossRef] [PubMed]
67. Capuron, L.; Miller, A.H. Cytokines and psychopathology: Lessons from interferon-alpha. *Biol. Psychiatry* **2004**, *56*, 819–824. [CrossRef]
68. Yirmiya, R. Behavioral and psychological effects of immune activation: Implications for "depression due to a general medical condition". *Curr. Opin. Psychiatry* **1997**, *10*, 470–476. [CrossRef]
69. Dunn, A.J.; Swiergiel, A.H.; de Beaurepaire, R. Cytokines as mediators of depression: What can we learn from animal studies? *Neurosci. Biobehav. Rev.* **2005**, *29*, 891–909. [CrossRef]
70. Goshen, I.; Yirmiya, R. Interleukin-1 (IL-1): A central regulator of stress responses. *Front. Neuroendocr.* **2009**, *30*, 30–45. [CrossRef]
71. Maes, M.; Berk, M.; Goehler, L.; Song, C.; Anderson, G.; Gałecki, P.; Leonard, B. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med.* **2012**, *10*, 66. [CrossRef]
72. Dubois, T.; Reynaert, C.; Jacques, D.; Lepiece, B.; Patigny, P.; Zdanowicz, N. Immunity and psychiatric disorders: Variabilities of immunity biomarkers are they specific? *Psychiatr. Danub.* **2018**, *30*, 447–451.

73. Danese, A.; Pariante, C.M.; Caspi, A.; Taylor, A.; Poulton, R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 1319–1324. [CrossRef] [PubMed]

74. Danese, A.; Moffitt, T.E.; Harrington, H.; Milne, B.J.; Polanczyk, G.; Pariante, C.M.; Poulton, R.; Caspi, A. Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. *Arch. Pediatr. Adolesc. Med.* **2009**, *163*, 1135–1143. [CrossRef] [PubMed]

75. Preez, A.D.; Leveson, J.; Zunszain, P.A.; Pariante, C.M. Inflammatory insults and mental health consequences: Does timing matter when it comes to depression? *Psychol. Med.* **2016**, *46*, 2041–2057. [CrossRef] [PubMed]

76. Schleifer, S.J.; Keller, S.E.; Meyerson, A.T.; Raskin, M.J.; Davis, K.L.; Stein, M. Lymphocyte function in major depressive disorder. *Arch. Gen. Psychiatry* **1984**, *41*, 484–486. [CrossRef]

77. Irwin, M.; Gillin, J.C. Impaired natural killer cell activity among depressed patients. *Psychiatry Res.* **1987**, *20*, 181–182. [CrossRef]

78. Maes, M.; Carvalho, A.F. The compensatory immune-regulatory reflex system (CIRS) in depression and bipolar disorder. *Mol. Neurobiol.* **2018**, *55*, 8885–8903. [CrossRef]

79. Maes, M.; Bosmans, E.; De Jongh, R.; Kenis, G.; Vandoolaeghe, E.; Neels, H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine* **1997**, *9*, 853–858. [CrossRef]

80. Maes, M.; Anderson, G.; Kubera, M.; Berk, M. Targeting classical IL-6 signalling or IL-6 trans-signalling in depression? *Expert Opin. Targets* **2014**, *18*, 495–512. [CrossRef]

81. Vanuytsel, T.; Vermeire, S.; Cleynen, I. The role of haptoglobin and its related protein, zonulin, in inflammatory bowel disease. *Tissue Barriers* **2013**, *1*. [CrossRef]

82. Walker, F.R. A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: Do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? *Neuropharmacology* **2013**, *67*, 304–317. [CrossRef]

83. Köhler, C.A.; Freitas, T.H.; Stubbs, B.; Maes, M.; Solmi, M.; Veronese, N.; de Andrade, N.Q.; Morris, G.; Fernandes, B.S.; Brunoni, A.R.; et al. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: Systematic review and meta-analysis. *Mol. Neurobiol.* **2018**, *55*, 4195–4206. [CrossRef] [PubMed]

84. Köhler, O.; Benros, M.E.; Nordentoft, M.; Farkouh, M.E.; Iyengar, R.L.; Mors, O.; Krogh, J. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: A systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* **2014**, *71*, 1381–1391. [CrossRef] [PubMed]

85. Kappelmann, N.; Lewis, G.; Dantzer, R.; Jones, P.B.; Khandaker, G.M. Antidepressant activity of anti-cytokine treatment: A systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol. Psychiatry* **2018**, *23*, 335–343. [CrossRef] [PubMed]

86. Norden, D.M.; McCarthy, D.O.; Bicer, S.; Devine, R.; Reiser, P.J.; Godbout, J.P.; Wold, L.E. Ibuprofen ameliorates fatigue- and depressive-like behavior in tumor-bearing mice. *Life Sci.* **2015**, *143*, 65–70. [CrossRef]

87. Liu, Y.; Ho, R.C.-M.; Mak, A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. *J. Affect. Disord.* **2012**, *139*, 230–239. [CrossRef]

88. Hiles, S.A.; Baker, A.L.; de Malmanche, T.; Attia, J. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: A meta-analysis. *Psychol. Med.* **2012**, *42*, 2015–2026. [CrossRef]

89. Valkanova, V.; Ebmeier, K.P.; Allan, C.L. CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *J. Affect. Disord.* **2013**, *150*, 736–744. [CrossRef]

90. Köhler, C.A.; Freitas, T.H.; Maes, M.; de Andrade, N.Q.; Liu, C.S.; Fernandes, B.S.; Stubbs, B.; Solmi, M.; Veronese, N.; Herrmann, N.; et al. Peripheral cytokine and chemokine alterations in depression: A meta-analysis of 82 studies. *Acta Psychiatr. Scand.* **2017**, *135*, 373–387. [CrossRef]

91. Schiepers, O.J.G.; Wichers, M.C.; Maes, M. Cytokines and major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2005**, *29*, 201–217. [CrossRef]

92. Gimeno, D.; Marmot, M.G.; Singh-Manoux, A. Inflammatory markers and cognitive function in middle-aged adults: The whitehall II study. *Psychoneuroendocrinology* **2008**, *33*, 1322–1334. [CrossRef]

93. Maes, M.; Scharpé, S.; Meltzer, H.Y.; Bosmans, E.; Suy, E.; Calabrese, J.; Cosyns, P. Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. *Psychiatry Res.* **1993**, *49*, 11–27. [CrossRef]

94. Cattaneo, A.; Gennarelli, M.; Uher, R.; Breen, G.; Farmer, A.; Aitchison, K.J.; Craig, I.W.; Anacker, C.; Zunsztain, P.A.; McGuffin, P.; et al. Candidate genes expression profile associated with antidepressants response in the GENDEP study: Differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology* **2013**, *38*, 377–385. [CrossRef] [PubMed]

95. Lehtimäki, K.; Keränen, T.; Huuhka, M.; Palmio, J.; Hurme, M.; Leinonen, E.; Peltola, J. Increase in plasma proinflammatory cytokines after electroconvulsive therapy in patients with depressive disorder. *J. ECT* **2008**, *24*, 88–91. [CrossRef] [PubMed]

96. Strawbridge, R.; Arnone, D.; Danese, A.; Papadopoulos, A.; Herane Vives, A.; Cleare, A.J. Inflammation and clinical response to treatment in depression: A meta-analysis. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* **2015**, *25*, 1532–1543. [CrossRef] [PubMed]

97. Rose-John, S. IL-6 Trans-Signaling via the soluble IL-6 receptor: Importance for the pro-inflammatory activities of IL-6. *Int. J. Biol. Sci.* **2012**, *8*, 1237–1247. [CrossRef] [PubMed]

98. Goldsmith, D.R.; Rapaport, M.H.; Miller, B.J. A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. *Mol. Psychiatry* **2016**, *21*, 1696–1709. [CrossRef]

99. Siwek, M.; Sowa-Kućma, M.; Styczeń, K.; Misztak, P.; Nowak, R.J.; Szewczyk, B.; Dudek, D.; Rybakowski, J.K.; Nowak, G.; Maes, M. Associations of serum cytokine receptor levels with melancholia, staging of illness, depressive and manic phases, and severity of depression in bipolar disorder. *Mol. Neurobiol.* **2017**, *54*, 5883–5893. [CrossRef]

100. Sowa-Kućma, M.; Styczeń, K.; Siwek, M.; Misztak, P.; Nowak, R.J.; Dudek, D.; Rybakowski, J.K.; Nowak, G.; Maes, M. Are there differences in lipid peroxidation and immune biomarkers between major depression and bipolar disorder: Effects of melancholia, atypical depression, severity of illness, episode number, suicidal ideation and prior suicide attempts. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2018**, *81*, 372–383. [CrossRef]

101. Prins, B.P.; Abbasi, A.; Wong, A.; Vaez, A.; Nolte, I.; Franceschini, N.; Stuart, P.E.; Achury, J.G.; Mistry, V.; Bradfield, J.P.; et al. Investigating the causal relationship of C-reactive protein with 32 complex somatic and psychiatric outcomes: A large-scale cross-consortium mendelian randomization study. *PLoS Med.* **2016**, *13*, e1001976. [CrossRef]

102. Ford, D.E.; Erlinger, T.P. Depression and C-reactive protein in US adults: Data from the third national health and nutrition examination survey. *Arch. Intern. Med.* **2004**, *164*, 1010–1014. [CrossRef]

103. Elovainio, M.; Aalto, A.-M.; Kivimäki, M.; Pirkola, S.; Sundvall, J.; Lönnqvist, J.; Reunanen, A. Depression and C-reactive protein: Population-based health 2000 study. *Psychosom. Med.* **2009**, *71*, 423–430. [CrossRef] [PubMed]

104. Liukkonen, T.; Räsänen, P.; Jokelainen, J.; Leinonen, M.; Järvelin, M.-R.; Meyer-Rochow, V.B.; Timonen, M. The association between anxiety and C-reactive protein (CRP) levels: Results from the northern finland 1966 birth cohort study. *Eur. Psychiatry J. Assoc. Eur. Psychiatr.* **2011**, *26*, 363–369. [CrossRef] [PubMed]

105. Hickman, R.J.; Khambaty, T.; Stewart, J.C. C-reactive protein is elevated in atypical but not nonatypical depression: Data from the national health and nutrition examination survey (NHANES) 1999–2004. *J. Behav. Med.* **2014**, *37*, 621–629. [CrossRef] [PubMed]

106. Duivis, H.E.; Vogelzangs, N.; Kupper, N.; de Jonge, P.; Penninx, B.W.J.H. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: Findings from The Netherlands study of depression and anxiety (NESDA). *Psychoneuroendocrinology* **2013**, *38*, 1573–1585. [CrossRef] [PubMed]

107. Miller, G.E.; Cole, S.W. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biol. Psychiatry* **2012**, *72*, 34–40. [CrossRef] [PubMed]

108. Copeland, W.E.; Shanahan, L.; Worthman, C.; Angold, A.; Costello, E.J. Cumulative depression episodes predict later C-reactive protein levels: A prospective analysis. *Biol. Psychiatry* **2012**, *71*, 15–21. [CrossRef] [PubMed]

109. Köhler-Forsberg, O.; Buttenschøn, H.N.; Tansey, K.E.; Maier, W.; Hauser, J.; Dernovsek, M.Z.; Henigsberg, N.; Souery, D.; Farmer, A.; Rietschel, M.; et al. Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. *Brain Behav. Immun.* **2017**, *62*, 344–350. [CrossRef]

110. Fernandes, B.S.; Steiner, J.; Molendijk, M.L.; Dodd, S.; Nardin, P.; Gonçalves, C.-A.; Jacka, F.; Köhler, C.A.; Karmakar, C.; Carvalho, A.F.; et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: A systematic review and meta-analysis. *Lancet Psychiatry* **2016**, *3*, 1147–1156. [CrossRef]

111. Wium-Andersen, M.K.; Ørsted, D.D.; Nielsen, S.F.; Nordestgaard, B.G. Elevated C-reactive protein levels, psychological distress, and depression in 73.131 individuals. *JAMA Psychiatry* **2013**, *70*, 176–184. [CrossRef]

112. Uher, R.; Tansey, K.E.; Dew, T.; Maier, W.; Mors, O.; Hauser, J.; Dernovsek, M.Z.; Henigsberg, N.; Souery, D.; Farmer, A.; et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *Am. J. Psychiatry* **2014**, *171*, 1278–1286. [CrossRef]

113. Jha, M.K.; Minhajuddin, A.; Gadad, B.S.; Greer, T.; Grannemann, B.; Soyombo, A.; Mayes, T.L.; Rush, A.J.; Trivedi, M.H. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology* **2017**, *78*, 105–113. [CrossRef] [PubMed]

114. Chang, H.H.; Lee, I.H.; Gean, P.W.; Lee, S.-Y.; Chi, M.H.; Yang, Y.K.; Lu, R.-B.; Chen, P.S. Treatment response and cognitive impairment in major depression: Association with C-reactive protein. *Brain Behav. Immun.* **2012**, *26*, 90–95. [CrossRef] [PubMed]

115. Lindqvist, D.; Dhabhar, F.S.; James, S.J.; Hough, C.M.; Jain, F.A.; Bersani, F.S.; Reus, V.I.; Verhoeven, J.E.; Epel, E.S.; Mahan, L.; et al. Oxidative stress, inflammation and treatment response in major depression. *Psychoneuroendocrinology* **2017**, *76*, 197–205. [CrossRef]

116. Harley, J.; Luty, S.; Carter, J.; Mulder, R.; Joyce, P. Elevated C-reactive protein in depression: A predictor of good long-term outcome with antidepressants and poor outcome with psychotherapy. *J. Psychopharmacol. Oxf. Engl.* **2010**, *24*, 625–626. [CrossRef]

117. Raison, C.L.; Rutherford, R.E.; Woolwine, B.J.; Shuo, C.; Schettler, P.; Drake, D.F.; Haroon, E.; Miller, A.H. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. *JAMA Psychiatry* **2013**, *70*, 31–41. [CrossRef]

118. Martins-de-Souza, D. Proteomics, metabolomics, and protein interactomics in the characterization of the molecular features of major depressive disorder. *Dialogues Clin. Neurosci.* **2014**, *16*, 63–73.

119. Park, D.I.; Turck, C.W. Interactome studies of psychiatric disorders. *Adv. Exp. Med. Biol.* **2019**, *1118*, 163–173. [CrossRef] [PubMed]

120. Ng, A.; Tam, W.W.; Zhang, M.W.; Ho, C.S.; Husain, S.F.; McIntyre, R.S.; Ho, R.C. IL-1β, IL-6, TNF- α and CRP in elderly patients with depression or Alzheimer's disease: Systematic review and meta-analysis. *Sci. Rep.* **2018**, *8*, 12050. [CrossRef] [PubMed]

121. Maes, M.; Mihaylova, I.; Kubera, M.; Ringel, K. Activation of cell-mediated immunity in depression: Association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2012**, *36*, 169–175. [CrossRef] [PubMed]

122. Liu, J.J.; Wei, Y.B.; Strawbridge, R.; Bao, Y.; Chang, S.; Shi, L.; Que, J.; Gadad, B.S.; Trivedi, M.H.; Kelsoe, J.R.; et al. Peripheral cytokine levels and response to antidepressant treatment in depression: A systematic review and meta-analysis. *Mol. Psychiatry* **2020**, *25*, 339–350. [CrossRef]

123. Hestad, K.A.; Tønseth, S.; Støen, C.D.; Ueland, T.; Aukrust, P. Raised plasma levels of tumor necrosis factor alpha in patients with depression: Normalization during electroconvulsive therapy. *J. ECT* **2003**, *19*, 183–188. [CrossRef] [PubMed]

124. Sedger, L.M.; McDermott, M.F. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants—Past, present and future. *Cytokine Growth Factor Rev.* **2014**, *25*, 453–472. [CrossRef] [PubMed]

125. Sowa-Kućma, M.; Styczeń, K.; Siwek, M.; Misztak, P.; Nowak, R.J.; Dudek, D.; Rybakowski, J.K.; Nowak, G.; Maes, M. Lipid peroxidation and immune biomarkers are associated with major depression and its phenotypes, including treatment-resistant depression and melancholia. *Neurotox. Res.* **2018**, *33*, 448–460. [CrossRef] [PubMed]

126. Janelidze, S.; Mattei, D.; Westrin, Å.; Träskman-Bendz, L.; Brundin, L. Cytokine levels in the blood may distinguish suicide attempters from depressed patients. *Brain Behav. Immun.* **2011**, *25*, 335–339. [CrossRef]

127. Iosif, R.E.; Ekdahl, C.T.; Ahlenius, H.; Pronk, C.J.H.; Bonde, S.; Kokaia, Z.; Jacobsen, S.-E.W.; Lindvall, O. Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis. *J. Neurosci. Off. J. Soc. Neurosci.* **2006**, *26*, 9703–9712. [CrossRef]

128. Kaneko, N.; Kudo, K.; Mabuchi, T.; Takemoto, K.; Fujimaki, K.; Wati, H.; Iguchi, H.; Tezuka, H.; Kanba, S. Suppression of cell proliferation by interferon-alpha through interleukin-1 production in adult rat dentate gyrus. *Neuropsychopharmacology* **2006**, *31*, 2619–2626. [CrossRef]

129. Buntinx, M.; Moreels, M.; Vandenabeele, F.; Lambrichts, I.; Raus, J.; Steels, P.; Stinissen, P.; Ameloot, M. Cytokine-induced cell death in human oligodendroglial cell lines: I. Synergistic effects of IFN-gamma and TNF-alpha on apoptosis. *J. Neurosci. Res.* **2004**, *76*, 834–845. [CrossRef]

130. Medina, S.; Martínez, M.; Hernanz, A. Antioxidants inhibit the human cortical neuron apoptosis induced by hydrogen peroxide, tumor necrosis factor alpha, dopamine and beta-amyloid peptide 1-42. *Free Radic. Res.* **2002**, *36*, 1179–1184. [CrossRef]

131. Stellwagen, D.; Malenka, R.C. Synaptic scaling mediated by glial TNF-alpha. *Nature* **2006**, *440*, 1054–1059. [CrossRef]

132. Sunico, C.R.; Portillo, F.; González-Forero, D.; Moreno-López, B. Nitric oxide-directed synaptic remodeling in the adult mammal CNS. *J. Neurosci.* **2005**, *25*, 1448–1458. [CrossRef]

133. De la Rosa, M.; Rutz, S.; Dorninger, H.; Scheffold, A. Interleukin-2 is essential for CD4 + CD25 + regulatory T cell function. *Eur. J. Immunol.* **2004**, *34*, 2480–2488. [CrossRef] [PubMed]

134. Thornton, A.M.; Donovan, E.E.; Piccirillo, C.A.; Shevach, E.M. Cutting edge: IL-2 is critically required for the in vitro activation of CD4 + CD25 + T cell suppressor function. *J. Immunol. Baltim. Md. 1950* **2004**, *172*, 6519–6523. [CrossRef] [PubMed]

135. Maes, M.; Bosmans, E.; Suy, E.; Vandervorst, C.; De Jonckheere, C.; Raus, J. Immune disturbances during major depression: Upregulated expression of interleukin-2 receptors. *Neuropsychobiology* **1990**, *24*, 115–120. [CrossRef] [PubMed]

136. Vanmaris, R.; Rijkers, G.T. Biological role of the soluble interleukin-2 receptor in sarcoidosis. *Sarcoidosis Vasc. Diffus. Lung Dis.* **2017**, *34*, 122–129. [CrossRef]

137. Talarowska, M.; Szemraj, J.; Gałecki, P. The role of interleukin genes in the course of depression. *Open Med. Wars. Pol.* **2016**, *11*, 41–48. [CrossRef]

138. Baune, B.T.; Smith, E.; Reppermund, S.; Air, T.; Samaras, K.; Lux, O.; Brodaty, H.; Sachdev, P.; Trollor, J.N. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: The prospective Sydney memory and aging study. *Psychoneuroendocrinology* **2012**, *37*, 1521–1530. [CrossRef]

139. Eyre, H.A.; Air, T.; Pradhan, A.; Johnston, J.; Lavretsky, H.; Stuart, M.J.; Baune, B.T. A meta-analysis of chemokines in major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2016**, *68*, 1–8. [CrossRef]

140. Müller, N.; Myint, A.-M.; Schwarz, M.J. The impact of neuroimmune dysregulation on neuroprotection and neurotoxicity in psychiatric disorders - relation to drug treatment. *Dialogues Clin. Neurosci.* **2009**, *11*, 319–332.

141. Udina, M.; Castellví, P.; Moreno-España, J.; Navinés, R.; Valdés, M.; Forns, X.; Langohr, K.; Solà, R.; Vieta, E.; Martín-Santos, R. Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. *J. Clin. Psychiatry* **2012**, *73*, 1128–1138. [CrossRef]

142. Capuron, L.; Raison, C.L.; Musselman, D.L.; Lawson, D.H.; Nemeroff, C.B.; Miller, A.H. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am. J. Psychiatry* **2003**, *160*, 1342–1345. [CrossRef]

143. Bonaccorso, S.; Marino, V.; Puzella, A.; Pasquini, M.; Biondi, M.; Artini, M.; Almerighi, C.; Verkerk, R.; Meltzer, H.; Maes, M. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J. Clin. Psychopharmacol.* **2002**, *22*, 86–90. [CrossRef] [PubMed]

144. Lotrich, F.E. Major depression during interferon-α treatment: Vulnerability and prevention. *Dialogues Clin. Neurosci.* **2009**, *11*, 417–425. [PubMed]

145. Gadad, B.S.; Jha, M.K.; Grannemann, B.D.; Mayes, T.L.; Trivedi, M.H. Proteomics profiling reveals inflammatory biomarkers of antidepressant treatment response: Findings from the CO-MED trial. *J. Psychiatr. Res.* **2017**, *94*, 1–6. [CrossRef] [PubMed]

146. Conboy, L.; Varea, E.; Castro, J.E.; Sakouhi-Ouertatani, H.; Calandra, T.; Lashuel, H.A.; Sandi, C. Macrophage migration inhibitory factor is critically involved in basal and fluoxetine-stimulated adult hippocampal cell proliferation and in anxiety, depression, and memory-related behaviors. *Mol. Psychiatry* **2011**, *16*, 533–547. [CrossRef] [PubMed]

147. Musil, R.; Schwarz, M.J.; Riedel, M.; Dehning, S.; Cerovecki, A.; Spellmann, I.; Arolt, V.; Müller, N. Elevated macrophage migration inhibitory factor and decreased transforming growth factor-beta levels in major depression–no influence of celecoxib treatment. *J. Affect. Disord.* **2011**, *134*, 217–225. [CrossRef]

148. Stelzhammer, V.; Haenisch, F.; Chan, M.K.; Cooper, J.D.; Steiner, J.; Steeb, H.; Martins-de-Souza, D.; Rahmoune, H.; Guest, P.C.; Bahn, S. Proteomic changes in serum of first onset, antidepressant drug-naïve major depression patients. *Int. J. Neuropsychopharmacol.* **2014**, *17*, 1599–1608. [CrossRef]

149. Maes, M.; Delange, J.; Ranjan, R.; Meltzer, H.Y.; Desnyder, R.; Cooremans, W.; Scharpé, S. Acute phase proteins in schizophrenia, mania and major depression: Modulation by psychotropic drugs. *Psychiatry Res.* **1997**, *66*, 1–11. [CrossRef]

150. Song, C.; Dinan, T.; Leonard, B.E. Changes in immunoglobulin, complement and acute phase protein levels in the depressed patients and normal controls. *J. Affect. Disord.* **1994**, *30*, 283–288. [CrossRef]

151. Lamers, F.; Bot, M.; Jansen, R.; Chan, M.K.; Cooper, J.D.; Bahn, S.; Penninx, B.W.J.H. Serum proteomic profiles of depressive subtypes. *Transl. Psychiatry* **2016**, *6*, e851. [CrossRef]

152. Kadriu, B.; Gold, P.W.; Luckenbaugh, D.A.; Lener, M.S.; Ballard, E.D.; Niciu, M.J.; Henter, I.D.; Park, L.T.; De Sousa, R.T.; Yuan, P.; et al. Acute ketamine administration corrects abnormal inflammatory bone markers in major depressive disorder. *Mol. Psychiatry* **2018**, *23*, 1626–1631. [CrossRef]

153. Lee, J.; Joo, E.-J.; Lim, H.-J.; Park, J.-M.; Lee, K.Y.; Park, A.; Seok, A.; Lee, H.; Kang, H.-G. Proteomic analysis of serum from patients with major depressive disorder to compare their depressive and remission statuses. *Psychiatry Investig.* **2015**, *12*, 249–259. [CrossRef] [PubMed]

154. Domenici, E.; Willé, D.R.; Tozzi, F.; Prokopenko, I.; Miller, S.; McKeown, A.; Brittain, C.; Rujescu, D.; Giegling, I.; Turck, C.W.; et al. Plasma protein biomarkers for depression and schizophrenia by multi analyte profiling of case-control collections. *PLoS ONE* **2010**, *5*, e9166. [CrossRef] [PubMed]

155. Abdel-Nasser, A.M.; Abd El-Azim, S.; Taal, E.; El-Badawy, S.A.; Rasker, J.J.; Valkenburg, H.A. Depression and depressive symptoms in rheumatoid arthritis patients: An analysis of their occurrence and determinants. *Br. J. Rheumatol.* **1998**, *37*, 391–397. [CrossRef]

156. Hiles, S.A.; Baker, A.L.; de Malmanche, T.; Attia, J. A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: Exploring the causes of heterogeneity. *Brain Behav. Immun.* **2012**, *26*, 1180–1188. [CrossRef] [PubMed]

157. Hoekstra, R.; van den Broek, W.W.; Fekkes, D.; Bruijn, J.A.; Mulder, P.G.; Pepplinkhuizen, L. Effect of electroconvulsive therapy on biopterin and large neutral amino acids in severe, medication-resistant depression. *Psychiatry Res.* **2001**, *103*, 115–123. [CrossRef]

158. Anderson, D.N.; Abou-Saleh, M.T.; Collins, J.; Hughes, K.; Cattell, R.J.; Hamon, C.G.; Blair, J.A.; Dewey, M.E. Pterin metabolism in depression: An extension of the amine hypothesis and possible marker of response to ECT. *Psychol. Med.* **1992**, *22*, 863–869. [CrossRef] [PubMed]

159. Çelik, C.; Erdem, M.; Cayci, T.; Ozdemir, B.; Akgul, E.; Kurt, Y.; Yaman, H.; Isintas, M.; Ozgen, F.; Ozsahin, A. The association between serum levels of neopterin and number of depressive episodes of major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2010**, *34*, 372–375. [CrossRef]

160. Ng, F.; Berk, M.; Dean, O.; Bush, A.I. Oxidative stress in psychiatric disorders: Evidence base and therapeutic implications. *Int. J. Neuropsychopharmacol.* **2008**, *11*, 851–876. [CrossRef]

161. Wang, X.; Michaelis, E.K. Selective neuronal vulnerability to oxidative stress in the brain. *Front. Aging Neurosci.* **2010**, *2*, 12. [CrossRef]

162. Maes, M.; Song, C.; Lin, A.; De Jongh, R.; Van Gastel, A.; Kenis, G.; Bosmans, E.; De Meester, I.; Benoy, I.; Neels, H.; et al. The effects of psychological stress on humans: Increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine* **1998**, *10*, 313–318. [CrossRef]

163. Moylan, S.; Berk, M.; Dean, O.M.; Samuni, Y.; Williams, L.J.; O'Neil, A.; Hayley, A.C.; Pasco, J.A.; Anderson, G.; Jacka, F.N.; et al. Oxidative & nitrosative stress in depression: Why so much stress? *Neurosci. Biobehav. Rev.* **2014**, *45*, 46–62. [CrossRef] [PubMed]

164. Liu, T.; Zhong, S.; Liao, X.; Chen, J.; He, T.; Lai, S.; Jia, Y. A meta-analysis of oxidative stress markers in depression. *PLoS ONE* **2015**, *10*, e0138904. [CrossRef]

165. Mokoena, M.L.; Harvey, B.H.; Viljoen, F.; Ellis, S.M.; Brink, C.B. Ozone exposure of flinders sensitive line rats is a rodent translational model of neurobiological oxidative stress with relevance for depression and antidepressant response. *Psychopharmacology* **2015**, *232*, 2921–2938. [CrossRef] [PubMed]

166. Wu, J.Q.; Kosten, T.R.; Zhang, X.Y. Free radicals, antioxidant defense systems, and schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2013**, *46*, 200–206. [CrossRef] [PubMed]

167. Lee, S.-Y.; Lee, S.-J.; Han, C.; Patkar, A.A.; Masand, P.S.; Pae, C.-U. Oxidative/nitrosative stress and antidepressants: Targets for novel antidepressants. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2013**, *46*, 224–235. [CrossRef]

168. Maes, M.; Galecki, P.; Chang, Y.S.; Berk, M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 676–692. [CrossRef]

169. Salim, S. Oxidative stress and the central nervous system. *J. Pharm. Exp.* **2017**, *360*, 201–205. [CrossRef]

170. Chiurchiù, V.; Orlacchio, A.; Maccarrone, M. Is modulation of oxidative stress an answer? The state of the art of redox therapeutic actions in neurodegenerative diseases. *Oxid. Med. Cell. Longev.* **2016**, *2016*, 7909380. [CrossRef]

171. Maes, M.; D'Haese, P.C.; Scharpé, S.; D'Hondt, P.; Cosyns, P.; De Broe, M.E. Hypozincemia in depression. *J. Affect. Disord.* **1994**, *31*, 135–140. [CrossRef]

172. Maes, M.; Verkerk, R.; Vandoolaeghe, E.; Van Hunsel, F.; Neels, H.; Wauters, A.; Demedts, P.; Scharpé, S. Serotonin-immune interactions in major depression: Lower serum tryptophan as a marker of an immune-inflammatory response. *Eur. Arch. Psychiatry Clin. Neurosci.* **1997**, *247*, 154–161. [CrossRef]

173. Maes, M.; Vandoolaeghe, E.; Neels, H.; Demedts, P.; Wauters, A.; Meltzer, H.Y.; Altamura, C.; Desnyder, R. Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness. *Biol. Psychiatry* **1997**, *42*, 349–358. [CrossRef]

174. Maes, M.; Smith, R.; Christophe, A.; Vandoolaeghe, E.; Van Gastel, A.; Neels, H.; Demedts, P.; Wauters, A.; Meltzer, H.Y. Lower serum high-density lipoprotein cholesterol (HDL-C) in major depression and in depressed men with serious suicidal attempts: Relationship with immune-inflammatory markers. *Acta Psychiatr. Scand.* **1997**, *95*, 212–221. [CrossRef] [PubMed]

175. Cumurcu, B.E.; Ozyurt, H.; Etikan, I.; Demir, S.; Karlidag, R. Total antioxidant capacity and total oxidant status in patients with major depression: Impact of antidepressant treatment. *Psychiatry Clin. Neurosci.* **2009**, *63*, 639–645. [CrossRef] [PubMed]

176. Gałecki, P.; Szemraj, J.; Bieńkiewicz, M.; Zboralski, K.; Gałecka, E. Oxidative stress parameters after combined fluoxetine and acetylsalicylic acid therapy in depressive patients. *Hum. Psychopharmacol.* **2009**, *24*, 277–286. [CrossRef] [PubMed]

177. Maes, M.; Mihaylova, I.; Kubera, M.; Uytterhoeven, M.; Vrydags, N.; Bosmans, E. Increased plasma peroxides and serum oxidized low density lipoprotein antibodies in major depression: Markers that further explain the higher incidence of neurodegeneration and coronary artery disease. *J. Affect. Disord.* **2010**, *125*, 287–294. [CrossRef]

178. Pinto, V.L.M.; Brunini, T.M.C.; Ferraz, M.R.; Okinga, A.; Mendes-Ribeiro, A.C. Depression and cardiovascular disease: Role of nitric oxide. *Cardiovasc. Hematol. Agents Med. Chem.* **2008**, *6*, 142–149. [CrossRef]

179. Dhir, A.; Kulkarni, S.K. Nitric oxide and major depression. *Nitric Oxide Biol. Chem.* **2011**, *24*, 125–131. [CrossRef]

180. Brand, S.J.; Möller, M.; Harvey, B.H. A review of biomarkers in mood and psychotic disorders: A dissection of clinical vs. preclinical correlates. *Curr. Neuropharmacol.* **2015**, *13*, 324–368. [CrossRef]

181. Scapagnini, G.; Davinelli, S.; Drago, F.; De Lorenzo, A.; Oriani, G. Antioxidants as antidepressants: Fact or fiction? *CNS Drugs* **2012**, *26*, 477–490. [CrossRef]

182. Kim, Y.-K.; Paik, J.-W.; Lee, S.-W.; Yoon, D.; Han, C.; Lee, B.-H. Increased plasma nitric oxide level associated with suicide attempt in depressive patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2006**, *30*, 1091–1096. [CrossRef]

183. Suzuki, E.; Yoshida, Y.; Shibuya, A.; Miyaoka, H. Nitric oxide involvement in depression during interferon-alpha therapy. *Int. J. Neuropsychopharmacol.* **2003**, *6*, 415–419. [CrossRef] [PubMed]

184. Chrapko, W.E.; Jurasz, P.; Radomski, M.W.; Lara, N.; Archer, S.L.; Le Mellédo, J.-M. Decreased platelet nitric oxide synthase activity and plasma nitric oxide metabolites in major depressive disorder. *Biol. Psychiatry* **2004**, *56*, 129–134. [CrossRef] [PubMed]

185. Jiménez-Fernández, S.; Gurpegui, M.; Díaz-Atienza, F.; Pérez-Costillas, L.; Gerstenberg, M.; Correll, C.U. Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: Results from a meta-analysis. *J. Clin. Psychiatry* **2015**, *76*, 1658–1667. [CrossRef] [PubMed]

186. Bilici, M.; Efe, H.; Köroğlu, M.A.; Uydu, H.A.; Bekaroğlu, M.; Değer, O. Antioxidative enzyme activities and lipid peroxidation in major depression: Alterations by antidepressant treatments. *J. Affect. Disord.* **2001**, *64*, 43–51. [CrossRef]

187. Gałecki, P.; Szemraj, J.; Bieńkiewicz, M.; Florkowski, A.; Gałecka, E. Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. *Pharm. Rep. PR* **2009**, *61*, 436–447. [CrossRef]

188. Kotan, V.O.; Sarandol, E.; Kirhan, E.; Ozkaya, G.; Kirli, S. Effects of long-term antidepressant treatment on oxidative status in major depressive disorder: A 24-week follow-up study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 1284–1290. [CrossRef]

189. Sarandol, A.; Sarandol, E.; Eker, S.S.; Erdinc, S.; Vatansever, E.; Kirli, S. Major depressive disorder is accompanied with oxidative stress: Short-term antidepressant treatment does not alter oxidative-antioxidative systems. *Hum. Psychopharmacol.* **2007**, *22*, 67–73. [CrossRef]

190. Kodydková, J.; Vávrová, L.; Zeman, M.; Jirák, R.; Macásek, J.; Stanková, B.; Tvrzická, E.; Zák, A. Antioxidative enzymes and increased oxidative stress in depressive women. *Clin. Biochem.* **2009**, *42*, 1368–1374. [CrossRef]

191. Stefanescu, C.; Ciobica, A. The relevance of oxidative stress status in first episode and recurrent depression. *J. Affect. Disord.* **2012**, *143*, 34–38. [CrossRef]

192. Herken, H.; Gurel, A.; Selek, S.; Armutcu, F.; Ozen, M.E.; Bulut, M.; Kap, O.; Yumru, M.; Savas, H.A.; Akyol, O. Adenosine deaminase, nitric oxide, superoxide dismutase, and xanthine oxidase in patients with major depression: Impact of antidepressant treatment. *Arch. Med. Res.* **2007**, *38*, 247–252. [CrossRef]

193. Rybka, J.; Kędziora-Kornatowska, K.; Banaś-Leżańska, P.; Majsterek, I.; Carvalho, L.A.; Cattaneo, A.; Anacker, C.; Kędziora, J. Interplay between the pro-oxidant and antioxidant systems and proinflammatory cytokine levels, in relation to iron metabolism and the erythron in depression. *Free Radic. Biol. Med.* **2013**, *63*, 187–194. [CrossRef] [PubMed]

194. Khanzode, S.D.; Dakhale, G.N.; Khanzode, S.S.; Saoji, A.; Palasodkar, R. Oxidative damage and major depression: The potential antioxidant action of selective serotonin re-uptake inhibitors. *Redox Rep. Commun. Free Radic. Res.* **2003**, *8*, 365–370. [CrossRef] [PubMed]

195. Szuster-Ciesielska, A.; Słotwińska, M.; Stachura, A.; Marmurowska-Michałowska, H.; Dubas-Slemp, H.; Bojarska-Junak, A.; Kandefer-Szerszeń, M. Accelerated apoptosis of blood leukocytes and oxidative stress in blood of patients with major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2008**, *32*, 686–694. [CrossRef] [PubMed]

196. Gałecki, P.; Gałecka, E.; Maes, M.; Chamielec, M.; Orzechowska, A.; Bobińska, K.; Lewiński, A.; Szemraj, J. The expression of genes encoding for COX-2, MPO, iNOS, and sPLA2-IIA in patients with recurrent depressive disorder. *J. Affect. Disord.* **2012**, *138*, 360–366. [CrossRef]

197. Mazereeuw, G.; Herrmann, N.; Andreazza, A.C.; Scola, G.; Ma, D.W.L.; Oh, P.I.; Lanctôt, K.L. Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. *Brain Behav. Immun.* **2017**, *60*, 136–141. [CrossRef]

198. Mazereeuw, G.; Herrmann, N.; Andreazza, A.C.; Khan, M.M.; Lanctôt, K.L. A meta-analysis of lipid peroxidation markers in major depression. *Neuropsychiatr. Dis. Treat.* **2015**, *11*, 2479–2491. [CrossRef]

199. Versace, A.; Andreazza, A.C.; Young, L.T.; Fournier, J.C.; Almeida, J.R.C.; Stiffler, R.S.; Lockovich, J.C.; Aslam, H.A.; Pollock, M.H.; Park, H.; et al. Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: Toward peripheral biomarkers of bipolar disorder. *Mol. Psychiatry* **2014**, *19*, 200–208. [CrossRef]

200. Kadiiska, M.B.; Gladen, B.C.; Baird, D.D.; Germolec, D.; Graham, L.B.; Parker, C.E.; Nyska, A.; Wachsman, J.T.; Ames, B.N.; Basu, S.; et al. Biomarkers of oxidative stress study II: Are oxidation products of lipids, proteins, and DNA markers of CCl4 poisoning? *Free Radic. Biol. Med.* **2005**, *38*, 698–710. [CrossRef]

201. Praticò, D.; Rokach, J.; Lawson, J.; FitzGerald, G.A. F2-isoprostanes as indices of lipid peroxidation in inflammatory diseases. *Chem. Phys. Lipids* **2004**, *128*, 165–171. [CrossRef]

202. Chung, C.P.; Schmidt, D.; Stein, C.M.; Morrow, J.D.; Salomon, R.M. Increased oxidative stress in patients with depression and its relationship to treatment. *Psychiatry Res.* **2013**, *206*, 213–216. [CrossRef]

203. Milaneschi, Y.; Cesari, M.; Simonsick, E.M.; Vogelzangs, N.; Kanaya, A.M.; Yaffe, K.; Patrignani, P.; Metti, A.; Kritchevsky, S.B.; Pahor, M.; et al. Lipid peroxidation and depressed mood in community-dwelling older men and women. *PLoS ONE* **2013**, *8*. [CrossRef] [PubMed]

204. Yager, S.; Forlenza, M.J.; Miller, G.E. Depression and oxidative damage to lipids. *Psychoneuroendocrinology* **2010**, *35*, 1356–1362. [CrossRef] [PubMed]

205. Dimopoulos, N.; Piperi, C.; Psarra, V.; Lea, R.W.; Kalofoutis, A. Increased plasma levels of 8-iso-PGF2alpha and IL-6 in an elderly population with depression. *Psychiatry Res.* **2008**, *161*, 59–66. [CrossRef] [PubMed]

206. Black, C.N.; Bot, M.; Scheffer, P.G.; Cuijpers, P.; Penninx, B.W.J.H. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology* **2015**, *51*, 164–175. [CrossRef]

207. Behr, G.A.; Moreira, J.C.F.; Frey, B.N. Preclinical and clinical evidence of antioxidant effects of antidepressant agents: Implications for the pathophysiology of major depressive disorder. *Oxid. Med. Cell. Longev.* **2012**, *2012*, 609421. [CrossRef]

208. Maes, M.; Mihaylova, I.; Leunis, J.-C. Increased serum IgM antibodies directed against phosphatidyl inositol (Pi) in chronic fatigue syndrome (CFS) and major depression: Evidence that an IgM-mediated immune response against Pi is one factor underpinning the comorbidity between both CFS and depression. *Neuro Endocrinol. Lett.* **2007**, *28*, 861–867.

209. Maes, M.; Mihaylova, I.; Kubera, M.; Leunis, J.-C.; Geffard, M. IgM-mediated autoimmune responses directed against multiple neoepitopes in depression: New pathways that underpin the inflammatory and neuroprogressive pathophysiology. *J. Affect. Disord.* **2011**, *135*, 414–418. [CrossRef]

210. Maes, M.; Kubera, M.; Leunis, J.-C.; Berk, M.; Geffard, M.; Bosmans, E. In depression, bacterial translocation may drive inflammatory responses, oxidative and nitrosative stress (O&NS), and autoimmune responses directed against O&NS-damaged neoepitopes. *Acta Psychiatr. Scand.* **2013**, *127*, 344–354. [CrossRef]

211. Maes, M.; Kubera, M.; Mihaylova, I.; Geffard, M.; Galecki, P.; Leunis, J.-C.; Berk, M. Increased autoimmune responses against auto-epitopes modified by oxidative and nitrosative damage in depression: Implications for the pathways to chronic depression and neuroprogression. *J. Affect. Disord.* **2013**, *149*, 23–29. [CrossRef]

212. Maes, M.; Mihaylova, I.; Kubera, M.; Leunis, J.-C. An IgM-mediated immune response directed against nitro-bovine serum albumin (nitro-BSA) in chronic fatigue syndrome (CFS) and major depression: Evidence that nitrosative stress is another factor underpinning the comorbidity between major depression and CFS. *Neuro Endocrinol. Lett.* **2008**, *29*, 313–319.

213. Wu, L.L.; Chiou, C.C.; Chang, P.Y.; Wu, J.T. Urinary 8-OHdG: A marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. *Clin. Chim. Acta Int. J. Clin. Chem.* **2004**, *339*, 1–9. [CrossRef] [PubMed]

214. Maes, M.; Mihaylova, I.; Kubera, M.; Uytterhoeven, M.; Vrydags, N.; Bosmans, E. Increased 8-hydroxy-deoxyguanosine, a marker of oxidative damage to DNA, in major depression and myalgic encephalomyelitis / chronic fatigue syndrome. *Neuro Endocrinol. Lett.* **2009**, *30*, 715–722.

215. Forlenza, M.J.; Miller, G.E. Increased serum levels of 8-hydroxy-2'-deoxyguanosine in clinical depression. *Psychosom. Med.* **2006**, *68*, 1–7. [CrossRef] [PubMed]

216. Jorgensen, A.; Krogh, J.; Miskowiak, K.; Bolwig, T.G.; Kessing, L.V.; Fink-Jensen, A.; Nordentoft, M.; Henriksen, T.; Weimann, A.; Poulsen, H.E.; et al. Systemic oxidatively generated DNA/RNA damage in clinical depression: Associations to symptom severity and response to electroconvulsive therapy. *J. Affect. Disord.* **2013**, *149*, 355–362. [CrossRef]

217. Berk, M.; Copolov, D.L.; Dean, O.; Lu, K.; Jeavons, S.; Schapkaitz, I.; Anderson-Hunt, M.; Bush, A.I. N-acetyl cysteine for depressive symptoms in bipolar disorder–a double-blind randomized placebo-controlled trial. *Biol. Psychiatry* **2008**, *64*, 468–475. [CrossRef] [PubMed]

218. Deepmala; Slattery, J.; Kumar, N.; Delhey, L.; Berk, M.; Dean, O.; Spielholz, C.; Frye, R. Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. *Neurosci. Biobehav. Rev.* **2015**, *55*, 294–321. [CrossRef]

219. Maes, M.; Mihaylova, I.; Kubera, M.; Uytterhoeven, M.; Vrydags, N.; Bosmans, E. Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. *Neuro Endocrinol. Lett.* **2009**, *30*, 470–476.

220. Styczeń, K.; Sowa-Kućma, M.; Siwek, M.; Dudek, D.; Reczyński, W.; Szewczyk, B.; Misztak, P.; Topór-Mądry, R.; Opoka, W.; Nowak, G. The serum zinc concentration as a potential biological marker in patients with major depressive disorder. *Metab. Brain Dis.* **2017**, *32*, 97–103. [CrossRef]

221. Parker, K.J.; Schatzberg, A.F.; Lyons, D.M. Neuroendocrine aspects of hypercortisolism in major depression. *Horm. Behav.* **2003**, *43*, 60–66. [CrossRef]

222. Stetler, C.; Miller, G.E. Depression and hypothalamic-pituitary-adrenal activation: A quantitative summary of four decades of research. *Psychosom. Med.* **2011**, *73*, 114–126. [CrossRef]

223. Goodyer, I.M.; Croudace, T.; Dudbridge, F.; Ban, M.; Herbert, J. Polymorphisms in BDNF (Val66Met) and 5-HTTLPR, morning cortisol and subsequent depression in at-risk adolescents. *Br. J. Psychiatry J. Ment. Sci.* **2010**, *197*, 365–371. [CrossRef]

224. Krishnan, V.; Nestler, E.J. The molecular neurobiology of depression. *Nature* **2008**, *455*, 894–902. [CrossRef]

225. Schatzberg, A.F.; Rothschild, A.J.; Bond, T.C.; Cole, J.O. The DST in psychotic depression: Diagnostic and pathophysiologic implications. *Psychopharmacol. Bull.* **1984**, *20*, 362–364.

226. Stewart, J.G.; Mazurka, R.; Bond, L.; Wynne-Edwards, K.E.; Harkness, K.L. Rumination and impaired cortisol recovery following a social stressor in adolescent depression. *J. Abnorm. Child Psychol.* **2013**, *41*, 1015–1026. [CrossRef]

227. Rao, P.; Benito, E.; Fischer, A. MicroRNAs as biomarkers for CNS disease. *Front. Mol. Neurosci.* **2013**, *6*. [CrossRef] [PubMed]

228. Anacker, C.; Zunszain, P.A.; Carvalho, L.A.; Pariante, C.M. The glucocorticoid receptor: Pivot of depression and of antidepressant treatment? *Psychoneuroendocrinology* **2011**, *36*, 415–425. [CrossRef] [PubMed]

229. Markopoulou, K.; Papadopoulos, A.; Juruena, M.F.; Poon, L.; Pariante, C.M.; Cleare, A.J. The ratio of cortisol/DHEA in treatment resistant depression. *Psychoneuroendocrinology* **2009**, *34*, 19–26. [CrossRef] [PubMed]

230. Lamers, F.; Vogelzangs, N.; Merikangas, K.R.; de Jonge, P.; Beekman, A.T.F.; Penninx, B.W.J.H. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol. Psychiatry* **2013**, *18*, 692–699. [CrossRef]

231. Pittenger, C.; Duman, R.S. Stress, depression, and neuroplasticity: A convergence of mechanisms. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **2008**, *33*, 88–109. [CrossRef]

232. Dranovsky, A.; Hen, R. Hippocampal neurogenesis: Regulation by stress and antidepressants. *Biol. Psychiatry* **2006**, *59*, 1136–1143. [CrossRef]

233. Swaab, D.F.; Bao, A.-M.; Lucassen, P.J. The stress system in the human brain in depression and neurodegeneration. *Ageing Res. Rev.* **2005**, *4*, 141–194. [CrossRef] [PubMed]

234. Carroll, B.J.; Curtis, G.C.; Mendels, J. Neuroendocrine regulation in depression. II. Discrimination of depressed from nondepressed patients. *Arch. Gen. Psychiatry* **1976**, *33*, 1051–1058. [CrossRef]

235. Carroll, B.J.; Feinberg, M.; Greden, J.F.; Tarika, J.; Albala, A.A.; Haskett, R.F.; James, N.M.; Kronfol, Z.; Lohr, N.; Steiner, M.; et al. A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. *Arch. Gen. Psychiatry* **1981**, *38*, 15–22. [CrossRef] [PubMed]

236. Arana, G.W.; Baldessarini, R.J.; Ornsteen, M. The dexamethasone suppression test for diagnosis and prognosis in psychiatry. Commentary and review. *Arch. Gen. Psychiatry* **1985**, *42*, 1193–1204. [CrossRef] [PubMed]

237. Ceulemans, D.L.; Westenberg, H.G.; van Praag, H.M. The effect of stress on the dexamethasone suppression test. *Psychiatry Res.* **1985**, *14*, 189–195. [CrossRef]

238. Holsboer, F.; Liebl, R.; Hofschuster, E. Repeated dexamethasone suppression test during depressive illness. Normalisation of test result compared with clinical improvement. *J. Affect. Disord.* **1982**, *4*, 93–101. [CrossRef]

239. Aubry, J.-M.; Gervasoni, N.; Osiek, C.; Perret, G.; Rossier, M.F.; Bertschy, G.; Bondolfi, G. The DEX/CRH neuroendocrine test and the prediction of depressive relapse in remitted depressed outpatients. *J. Psychiatr. Res.* **2007**, *41*, 290–294. [CrossRef]

240. Arborelius, L.; Owens, M.J.; Plotsky, P.M.; Nemeroff, C.B. The role of corticotropin-releasing factor in depression and anxiety disorders. *J. Endocrinol.* **1999**, *160*, 1–12. [CrossRef]

241. Raadsheer, F.C.; van Heerikhuize, J.J.; Lucassen, P.J.; Hoogendijk, W.J.; Tilders, F.J.; Swaab, D.F. Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. *Am. J. Psychiatry* **1995**, *152*, 1372–1376. [CrossRef]

242. Austin, M.C.; Janosky, J.E.; Murphy, H.A. Increased corticotropin-releasing hormone immunoreactivity in monoamine-containing pontine nuclei of depressed suicide men. *Mol. Psychiatry* **2003**, *8*, 324–332. [CrossRef]

243. Brouwer, J.P.; Appelhof, B.C.; van Rossum, E.F.C.; Koper, J.W.; Fliers, E.; Huyser, J.; Schene, A.H.; Tijssen, J.G.P.; Van Dyck, R.; Lamberts, S.W.J.; et al. Prediction of treatment response by HPA-axis and glucocorticoid receptor polymorphisms in major depression. *Psychoneuroendocrinology* **2006**, *31*, 1154–1163. [CrossRef] [PubMed]

244. Wysokiński, A.; Kłoszewska, I. Level of thyroid-stimulating hormone (TSH) in patients with acute schizophrenia, unipolar depression or bipolar disorder. *Neurochem. Res.* **2014**, *39*, 1245–1253. [CrossRef] [PubMed]

245. Joffe, R.T.; Pearce, E.N.; Hennessey, J.V.; Ryan, J.J.; Stern, R.A. Subclinical hypothyroidism, mood, and cognition in the elderly: A review. *Int. J. Geriatr. Psychiatry* **2013**, *28*, 111–118. [CrossRef] [PubMed]

246. Sekula, L.K.; Lucke, J.F.; Heist, E.K.; Czambel, R.K.; Rubin, R.T. Neuroendocrine aspects of primary endogenous depression. XV: Mathematical modeling of nocturnal melatonin secretion in major depressives and normal controls. *Psychiatry Res.* **1997**, *69*, 143–153. [CrossRef]

247. Khaleghipour, S.; Masjedi, M.; Ahade, H.; Enayate, M.; Pasha, G.; Nadery, F.; Ahmadzade, G. Morning and nocturnal serum melatonin rhythm levels in patients with major depressive disorder: An analytical cross-sectional study. *Sao Paulo Med. J. Rev. Paul. Med.* **2012**, *130*, 167–172. [CrossRef] [PubMed]

248. Buckley, T.M.; Schatzberg, A.F. A pilot study of the phase angle between cortisol and melatonin in major depression—A potential biomarker? *J. Psychiatr. Res.* **2010**, *44*, 69–74. [CrossRef] [PubMed]

249. Herman, A.P.; Bochenek, J.; Król, K.; Krawczyńska, A.; Antushevich, H.; Pawlina, B.; Herman, A.; Romanowicz, K.; Tomaszewska-Zaremba, D. Central interleukin-1β suppresses the nocturnal secretion of melatonin. *Mediat. Inflamm.* **2016**, *2016*, 2589483. [CrossRef]

250. Clark-Raymond, A.; Halaris, A. VEGF and depression: A comprehensive assessment of clinical data. *J. Psychiatr. Res.* **2013**, *47*, 1080–1087. [CrossRef]

251. Castrén, E.; Rantamäki, T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Dev. Neurobiol.* **2010**, *70*, 289–297. [CrossRef]

252. Malberg, J.E.; Monteggia, L.M. VGF, a new player in antidepressant action? *Sci. Signal.* **2008**, *1*, pe19. [CrossRef]

253. Turner, C.A.; Akil, H.; Watson, S.J.; Evans, S.J. The fibroblast growth factor system and mood disorders. *Biol. Psychiatry* **2006**, *59*, 1128–1135. [CrossRef] [PubMed]

254. Hanson, N.D.; Owens, M.J.; Nemeroff, C.B. Depression, antidepressants, and neurogenesis: A critical reappraisal. *Neuropsychopharmacology* **2011**, *36*, 2589–2602. [CrossRef] [PubMed]

255. Karege, F.; Perret, G.; Bondolfi, G.; Schwald, M.; Bertschy, G.; Aubry, J.-M. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res.* **2002**, *109*, 143–148. [CrossRef]

256. Dwivedi, Y.; Rizavi, H.S.; Roberts, R.C.; Conley, R.C.; Tamminga, C.A.; Pandey, G.N. Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. *J. Neurochem.* **2001**, *77*, 916–928. [CrossRef] [PubMed]

257. Aydemir, C.; Yalcin, E.S.; Aksaray, S.; Kisa, C.; Yildirim, S.G.; Uzbay, T.; Goka, E. Brain-derived neurotrophic factor (BDNF) changes in the serum of depressed women. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2006**, *30*, 1256–1260. [CrossRef]

258. Brunoni, A.R.; Lopes, M.; Fregni, F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: Implications for the role of neuroplasticity in depression. *Int. J. Neuropsychopharmacol.* **2008**, *11*, 1169–1180. [CrossRef]

259. Sen, S.; Duman, R.; Sanacora, G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: Meta-analyses and implications. *Biol. Psychiatry* **2008**, *64*, 527–532. [CrossRef]

260. Molendijk, M.L.; Spinhoven, P.; Polak, M.; Bus, B.A.A.; Penninx, B.W.J.H.; Elzinga, B.M. Serum BDNF concentrations as peripheral manifestations of depression: Evidence from a systematic review and meta-analyses on 179 associations (N = 9484). *Mol. Psychiatry* **2014**, *19*, 791–800. [CrossRef]

261. Flensborg-Madsen, T.; von Scholten, M.B.; Flachs, E.M.; Mortensen, E.L.; Prescott, E.; Tolstrup, J.S. Tobacco smoking as a risk factor for depression. A 26-year population-based follow-up study. *J. Psychiatr. Res.* **2011**, *45*, 143–149. [CrossRef]

262. Golden, S.H.; Lazo, M.; Carnethon, M.; Bertoni, A.G.; Schreiner, P.J.; Roux, A.V.D.; Lee, H.B.; Lyketsos, C. Examining a bidirectional association between depressive symptoms and diabetes. *JAMA J. Am. Med. Assoc.* **2008**, *299*, 2751–2759. [CrossRef]

263. Hong, W.; Fan, J.; Yuan, C.; Zhang, C.; Hu, Y.; Peng, D.; Wang, Y.; Huang, J.; Li, Z.; Yu, S.; et al. Significantly decreased mRNA levels of BDNF and MEK1 genes in treatment-resistant depression. *Neuroreport* **2014**, *25*, 753–755. [CrossRef] [PubMed]

264. Li, Y.-J.; Xu, M.; Gao, Z.-H.; Wang, Y.-Q.; Yue, Z.; Zhang, Y.-X.; Li, X.-X.; Zhang, C.; Xie, S.-Y.; Wang, P.-Y. Alterations of serum levels of BDNF-related miRNAs in patients with depression. *PLoS ONE* **2013**, *8*, e63648. [CrossRef] [PubMed]

265. Fernandes, B.S.; Berk, M.; Turck, C.W.; Steiner, J.; Gonçalves, C.-A. Decreased peripheral brain-derived neurotrophic factor levels are a biomarker of disease activity in major psychiatric disorders: A comparative meta-analysis. *Mol. Psychiatry* **2014**, *19*, 750–751. [CrossRef]

266. Kunugi, H.; Hori, H.; Adachi, N.; Numakawa, T. Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression. *Psychiatry Clin. Neurosci.* **2010**, *64*, 447–459. [CrossRef] [PubMed]

267. Fernandes, B.S.; Gama, C.S.; Ceresér, K.M.; Yatham, L.N.; Fries, G.R.; Colpo, G.; de Lucena, D.; Kunz, M.; Gomes, F.A.; Kapczinski, F. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: A systematic review and meta-regression analysis. *J. Psychiatr. Res.* **2011**, *45*, 995–1004. [CrossRef] [PubMed]

268. Du, Y.; Wu, H.-T.; Qin, X.-Y.; Cao, C.; Liu, Y.; Cao, Z.-Z.; Cheng, Y. Postmortem brain, cerebrospinal fluid, and blood neurotrophic factor levels in Alzheimer's disease: A systematic review and meta-analysis. *J. Mol. Neurosci. MN* **2018**, *65*, 289–300. [CrossRef]

269. Blugeot, A.; Rivat, C.; Bouvier, E.; Molet, J.; Mouchard, A.; Zeau, B.; Bernard, C.; Benoliel, J.-J.; Becker, C. Vulnerability to depression: From brain neuroplasticity to identification of biomarkers. *J. Neurosci.* **2011**, *31*, 12889–12899. [CrossRef]

270. Cannon, T.D.; van Erp, T.G.M.; Bearden, C.E.; Loewy, R.; Thompson, P.; Toga, A.W.; Huttunen, M.O.; Keshavan, M.S.; Seidman, L.J.; Tsuang, M.T. Early and late neurodevelopmental influences in the prodrome to schizophrenia: Contributions of genes, environment, and their interactions. *Schizophr. Bull.* **2003**, *29*, 653–669. [CrossRef]

271. Huang, T.L.; Lee, C.T.; Liu, Y.L. Serum brain-derived neurotrophic factor levels in patients with major depression: Effects of antidepressants. *J. Psychiatr. Res.* **2007**, *42*, 521–525. [CrossRef]

272. Dwivedi, Y.; Rizavi, H.S.; Conley, R.R.; Roberts, R.C.; Tamminga, C.A.; Pandey, G.N. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch. Gen. Psychiatry* **2003**, *60*, 804–815. [CrossRef]

273. Nibuya, M.; Morinobu, S.; Duman, R.S. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J. Neurosci. Off. J. Soc. Neurosci.* **1995**, *15*, 7539–7547. [CrossRef]

274. Brunoni, A.R.; Baeken, C.; Machado-Vieira, R.; Gattaz, W.F.; Vanderhasselt, M.-A. BDNF blood levels after electroconvulsive therapy in patients with mood disorders: A systematic review and meta-analysis. *World J. Biol. Psychiatry Off. J. World Fed. Soc. Biol. Psychiatry* **2014**, *15*, 411–418. [CrossRef] [PubMed]

275. Polyakova, M.; Stuke, K.; Schuemberg, K.; Mueller, K.; Schoenknecht, P.; Schroeter, M.L. BDNF as a biomarker for successful treatment of mood disorders: A systematic & quantitative meta-analysis. *J. Affect. Disord.* **2015**, *174*, 432–440. [CrossRef] [PubMed]

276. Mill, J.; Petronis, A. Molecular studies of major depressive disorder: The epigenetic perspective. *Mol. Psychiatry* **2007**, *12*, 799–814. [CrossRef] [PubMed]

277. Sahay, A.; Hen, R. Adult hippocampal neurogenesis in depression. *Nat. Neurosci.* **2007**, *10*, 1110–1115. [CrossRef]

278. Tu, K.-Y.; Wu, M.-K.; Chen, Y.-W.; Lin, P.-Y.; Wang, H.-Y.; Wu, C.-K.; Tseng, P.-T. Significantly higher peripheral insulin-like growth factor-1 levels in patients with major depressive disorder or bipolar disorder than in healthy controls. *Medicine* **2016**, *95*. [CrossRef]

279. Anderson, M.F.; Aberg, M.A.I.; Nilsson, M.; Eriksson, P.S. Insulin-like growth factor-I and neurogenesis in the adult mammalian brain. *Brain Res. Dev. Brain Res.* **2002**, *134*, 115–122. [CrossRef]

280. Aberg, M.A.; Aberg, N.D.; Hedbäcker, H.; Oscarsson, J.; Eriksson, P.S. Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. *J. Neurosci. Off. J. Soc. Neurosci.* **2000**, *20*, 2896–2903. [CrossRef]

281. Park, S.-E.; Dantzer, R.; Kelley, K.W.; McCusker, R.H. Central administration of insulin-like growth factor-I decreases depressive-like behavior and brain cytokine expression in mice. *J. Neuroinflammation* **2011**, *8*, 12. [CrossRef]

282. Duman, C.H.; Schlesinger, L.; Terwilliger, R.; Russell, D.S.; Newton, S.S.; Duman, R.S. Peripheral insulin-like growth factor-I produces antidepressant-like behavior and contributes to the effect of exercise. *Behav. Brain Res.* **2009**, *198*, 366–371. [CrossRef]

283. Palmer, T.D.; Willhoite, A.R.; Gage, F.H. Vascular niche for adult hippocampal neurogenesis. *J. Comp. Neurol.* **2000**, *425*, 479–494. [CrossRef]

284. Carvalho, A.F.; Köhler, C.A.; McIntyre, R.S.; Knöchel, C.; Brunoni, A.R.; Thase, M.E.; Quevedo, J.; Fernandes, B.S.; Berk, M. Peripheral vascular endothelial growth factor as a novel depression biomarker: A meta-analysis. *Psychoneuroendocrinology* **2015**, *62*, 18–26. [CrossRef] [PubMed]

285. Tseng, P.-T.; Cheng, Y.-S.; Chen, Y.-W.; Wu, C.-K.; Lin, P.-Y. Increased levels of vascular endothelial growth factor in patients with major depressive disorder: A meta-analysis. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* **2015**, *25*, 1622–1630. [CrossRef] [PubMed]

286. Iga, J.I.; Ueno, S.I.; Yamauchi, K.; Numata, S.; Tayoshi-Shibuya, S.; Kinouchi, S.; Nakataki, M.; Song, H.; Hokoishi, K.; Tanabe, H.; et al. Gene expression and association analysis of vascular endothelial growth factor in major depressive disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2006**, *31*, 658–663. [CrossRef] [PubMed]

287. Wu, C.-K.; Tseng, P.-T.; Chen, Y.-W.; Tu, K.-Y.; Lin, P.-Y. Significantly higher peripheral fibroblast growth factor-2 levels in patients with major depressive disorder: A preliminary meta-analysis under MOOSE guidelines. *Medicine* **2016**, *95*, e4563. [CrossRef]

288. Jarosik, J.; Legutko, B.; Werner, S.; Unsicker, K.; von Bohlen und Halbach, O. Roles of exogenous and endogenous FGF-2 in animal models of depression. *Restor. Neurol. Neurosci.* **2011**, *29*, 153–165. [CrossRef]

289. Audet, M.-C.; Anisman, H. Interplay between pro-inflammatory cytokines and growth factors in depressive illnesses. *Front. Cell. Neurosci.* **2013**, *7*. [CrossRef]

290. Cattaneo, A.; Sesta, A.; Calabrese, F.; Nielsen, G.; Riva, M.A.; Gennarelli, M. The expression of VGF is reduced in leukocytes of depressed patients and it is restored by effective antidepressant treatment. *Neuropsychopharmacology* **2010**, *35*, 1423–1428. [CrossRef]

291. Virkkunen, M.; Goldman, D.; Nielsen, D.A.; Linnoila, M. Low brain serotonin turnover rate (low CSF 5-HIAA) and impulsive violence. *J. Psychiatry Neurosci.* **1995**, *20*, 271–275.

292. Lidberg, L.; Tuck, J.R.; Asberg, M.; Scalia-Tomba, G.P.; Bertilsson, L. Homicide, suicide and CSF 5-HIAA. *Acta Psychiatr. Scand.* **1985**, *71*, 230–236. [CrossRef]

293. Kaufman, J.; DeLorenzo, C.; Choudhury, S.; Parsey, R.V. The 5-HT1A receptor in major depressive disorder. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* **2016**, *26*, 397–410. [CrossRef] [PubMed]

294. Wang, L.; Zhou, C.; Zhu, D.; Wang, X.; Fang, L.; Zhong, J.; Mao, Q.; Sun, L.; Gong, X.; Xia, J.; et al. Serotonin-1A receptor alterations in depression: A meta-analysis of molecular imaging studies. *BMC Psychiatry* **2016**, *16*, 319. [CrossRef] [PubMed]

295. Maes, M.; Ringel, K.; Kubera, M.; Berk, M.; Rybakowski, J. Increased autoimmune activity against 5-HT: A key component of depression that is associated with inflammation and activation of cell-mediated immunity, and with severity and staging of depression. *J. Affect. Disord.* **2012**, *136*, 386–392. [CrossRef] [PubMed]

296. Mendelson, S.D. The current status of the platelet 5-HT(2A) receptor in depression. *J. Affect. Disord.* **2000**, *57*, 13–24. [CrossRef]

297. Nestler, E.J.; Carlezon, W.A. The mesolimbic dopamine reward circuit in depression. *Biol. Psychiatry* **2006**, *59*, 1151–1159. [CrossRef]

298. Moret, C.; Briley, M. The importance of norepinephrine in depression. *Neuropsychiatr. Dis. Treat.* **2011**, *7*, 9–13. [CrossRef]

299. Hughes, J.W.; Watkins, L.; Blumenthal, J.A.; Kuhn, C.; Sherwood, A. Depression and anxiety symptoms are related to increased 24-hour urinary norepinephrine excretion among healthy middle-aged women. *J. Psychosom. Res.* **2004**, *57*, 353–358. [CrossRef]

300. Mooney, J.J.; Samson, J.A.; Hennen, J.; Pappalardo, K.; McHale, N.; Alpert, J.; Koutsos, M.; Schildkraut, J.J. Enhanced norepinephrine output during longterm desipramine treatment: A possible role for the extraneuronal monoamine transporter (SLC22A3). *J. Psychiatr. Res.* **2008**, *42*, 605–611. [CrossRef]

301. Zeb, F.; Naqvi, S.; Rahman, R.; Farooq, A.D. Depressive symptoms, monoamines levels, MAO-B activity and effect of treatment in a subset of depressed individuals from government sector hospital at Karachi. *Pak. J. Pharm. Sci.* **2017**, *30*, 1509–1519.

302. Hashimoto, K. Emerging role of glutamate in the pathophysiology of major depressive disorder. *Brain Res. Rev.* **2009**, *61*, 105–123. [CrossRef]

303. Coyle, J.T.; Puttfarcken, P. Oxidative stress, glutamate, and neurodegenerative disorders. *Science* **1993**, *262*, 689–695. [CrossRef] [PubMed]

304. Suzuki, E.; Yagi, G.; Nakaki, T.; Kanba, S.; Asai, M. Elevated plasma nitrate levels in depressive states. *J. Affect. Disord.* **2001**, *63*, 221–224. [CrossRef]

305. Zarate, C.A.; Du, J.; Quiroz, J.; Gray, N.A.; Denicoff, K.D.; Singh, J.; Charney, D.S.; Manji, H.K. Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: Role of the glutamatergic system. *Ann. N. Y. Acad. Sci.* **2003**, *1003*, 273–291. [CrossRef] [PubMed]

306. Inoshita, M.; Umehara, H.; Watanabe, S.; Nakataki, M.; Kinoshita, M.; Tomioka, Y.; Tajima, A.; Numata, S.; Ohmori, T. Elevated peripheral blood glutamate levels in major depressive disorder. *Neuropsychiatr. Dis. Treat.* **2018**, *14*, 945–953. [CrossRef]

307. Harvey, B.H. Is major depressive disorder a metabolic encephalopathy? *Hum. Psychopharmacol.* **2008**, *23*, 371–384. [CrossRef]

308. Bak, L.K.; Schousboe, A.; Waagepetersen, H.S. The glutamate/GABA-glutamine cycle: Aspects of transport, neurotransmitter homeostasis and ammonia transfer. *J. Neurochem.* **2006**, *98*, 641–653. [CrossRef]

309. Petty, F.; Steinberg, J.; Kramer, G.L.; Fulton, M.; Moeller, F.G. Desipramine does not alter plasma GABA in patients with major depression. *J. Affect. Disord.* **1993**, *29*, 53–56. [CrossRef]

310. Petty, F.; Kramer, G.L.; Fulton, M.; Davis, L.; Rush, A.J. Stability of plasma GABA at four-year follow-up in patients with primary unipolar depression. *Biol. Psychiatry* **1995**, *37*, 806–810. [CrossRef]

311. Küçükibrahimoğlu, E.; Saygın, M.Z.; Çalışkan, M.; Kaplan, O.K.; Ünsal, C.; Gören, M.Z. The change in plasma GABA, glutamine and glutamate levels in fluoxetine- or S-citalopram-treated female patients with major depression. *Eur. J. Clin. Pharm.* **2009**, *65*, 571–577. [CrossRef]

312. Horrobin, D. Phospholipid metabolism and depression: The possible roles of phospholipase A2 and coenzyme A-independent transacylase. *Hum. Psychopharmacol.* **2001**, *16*, 45–52. [CrossRef]

313. Parekh, A.; Smeeth, D.; Milner, Y.; Thuret, S. The role of lipid biomarkers in major depression. *Healthcare* **2017**, *5*, 5. [CrossRef] [PubMed]

314. Liu, X.; Li, J.; Zheng, P.; Zhao, X.; Zhou, C.; Hu, C.; Hou, X.; Wang, H.; Xie, P.; Xu, G. Plasma lipidomics reveals potential lipid markers of major depressive disorder. *Anal. Bioanal. Chem.* **2016**, *408*, 6497–6507. [CrossRef] [PubMed]

315. Müller, C.P.; Reichel, M.; Mühle, C.; Rhein, C.; Gulbins, E.; Kornhuber, J. Brain membrane lipids in major depression and anxiety disorders. *Biochim. Biophys. Acta* **2015**, *1851*, 1052–1065. [CrossRef] [PubMed]

316. Bjerkeset, O.; Romundstad, P.; Evans, J.; Gunnell, D. Association of adult body mass index and height with anxiety, depression, and suicide in the general population: The HUNT study. *Am. J. Epidemiol.* **2008**, *167*, 193–202. [CrossRef] [PubMed]

317. Luppino, F.S.; de Wit, L.M.; Bouvy, P.F.; Stijnen, T.; Cuijpers, P.; Penninx, B.W.J.H.; Zitman, F.G. Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Arch. Gen. Psychiatry* **2010**, *67*, 220–229. [CrossRef] [PubMed]

318. Horrobin, D.F.; Bennett, C.N. Depression and bipolar disorder: Relationships to impaired fatty acid and phospholipid metabolism and to diabetes, cardiovascular disease, immunological abnormalities, cancer, ageing and osteoporosis. Possible candidate genes. *Prostaglandins Leukot. Essent. Fat. Acids* **1999**, *60*, 217–234. [CrossRef] [PubMed]

319. Lin, P.-Y.; Huang, S.-Y.; Su, K.-P. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol. Psychiatry* **2010**, *68*, 140–147. [CrossRef]

320. Maes, M.; Christophe, A.; Delanghe, J.; Altamura, C.; Neels, H.; Meltzer, H.Y. Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res.* **1999**, *85*, 275–291. [CrossRef]

321. Edwards, R.; Peet, M.; Shay, J.; Horrobin, D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J. Affect. Disord.* **1998**, *48*, 149–155. [CrossRef]

322. Maes, M.; Smith, R.; Christophe, A.; Cosyns, P.; Desnyder, R.; Meltzer, H. Fatty acid composition in major depression: Decreased ω3 fractions in cholesteryl esters and increased C20:4ω6C20:5ω3 ratio in cholesteryl esters and phospholipids. *J. Affect. Disord.* **1996**, *38*, 35–46. [CrossRef]

323. Appleton, K.M.; Rogers, P.J.; Ness, A.R. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *Am. J. Clin. Nutr.* **2010**, *91*, 757–770. [CrossRef] [PubMed]

324. Shin, J.Y.; Suls, J.; Martin, R. Are cholesterol and depression inversely related? A meta-analysis of the association between two cardiac risk factors. *Ann. Behav. Med. Publ. Soc. Behav. Med.* **2008**, *36*, 33–43. [CrossRef] [PubMed]

325. Olusi, S.O.; Fido, A.A. Serum lipid concentrations in patients with major depressive disorder. *Biol. Psychiatry* **1996**, *40*, 1128–1131. [CrossRef]

326. Akbaraly, T.N.; Ancelin, M.-L.; Jaussent, I.; Ritchie, C.; Barberger-Gateau, P.; Dufouil, C.; Kivimaki, M.; Berr, C.; Ritchie, K. Metabolic syndrome and onset of depressive symptoms in the elderly: Findings from the three-city study. *Diabetes Care* **2011**, *34*, 904–909. [CrossRef] [PubMed]

327. Demirkan, A.; Isaacs, A.; Ugocsai, P.; Liebisch, G.; Struchalin, M.; Rudan, I.; Wilson, J.F.; Pramstaller, P.P.; Gyllensten, U.; Campbell, H.; et al. Plasma phosphatidylcholine and sphingomyelin concentrations are associated with depression and anxiety symptoms in a Dutch family-based lipidomics study. *J. Psychiatr. Res.* **2013**, *47*, 357–362. [CrossRef]

328. Machado-Vieira, R.; Gold, P.W.; Luckenbaugh, D.A.; Ballard, E.D.; Richards, E.M.; Henter, I.D.; De Sousa, R.T.; Niciu, M.J.; Yuan, P.; Zarate, C.A. The role of adipokines in the rapid antidepressant effects of ketamine. *Mol. Psychiatry* **2017**, *22*, 127–133. [CrossRef]

329. Lu, X.-Y. The leptin hypothesis of depression: A potential link between mood disorders and obesity? *Curr. Opin. Pharm.* **2007**, *7*, 648–652. [CrossRef]

330. Wittekind, D.A.; Kluge, M. Ghrelin in psychiatric disorders—A review. *Psychoneuroendocrinology* **2015**, *52*, 176–194. [CrossRef]

331. Cizza, G.; Nguyen, V.T.; Eskandari, F.; Duan, Z.; Wright, E.C.; Reynolds, J.C.; Ahima, R.S.; Blackman, M.R. POWER Study Group Low 24-hour adiponectin and high nocturnal leptin concentrations in a case-control study of community-dwelling premenopausal women with major depressive disorder: The premenopausal, osteopenia/osteoporosis, women, alendronate, depression (POWER) study. *J. Clin. Psychiatry* **2010**, *71*, 1079–1087. [CrossRef]

332. Jow, G.-M.; Yang, T.-T.; Chen, C.-L. Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. *J. Affect. Disord.* **2006**, *90*, 21–27. [CrossRef]

333. Barim, A.O.; Aydin, S.; Colak, R.; Dag, E.; Deniz, O.; Sahin, I. Ghrelin, paraoxonase and arylesterase levels in depressive patients before and after citalopram treatment. *Clin. Biochem.* **2009**, *42*, 1076–1081. [CrossRef] [PubMed]

334. Tashiro, A.; Hongo, M.; Ota, R.; Utsumi, A.; Imai, T. Hyper-insulin response in a patient with depression. Changes in insulin resistance during recovery from depression. *Diabetes Care* **1997**, *20*, 1924–1925. [CrossRef] [PubMed]

335. Kan, C.; Silva, N.; Golden, S.H.; Rajala, U.; Timonen, M.; Stahl, D.; Ismail, K. A systematic review and meta-analysis of the association between depression and insulin resistance. *Diabetes Care* **2013**, *36*, 480–489. [CrossRef] [PubMed]

336. Lustman, P.J.; Anderson, R.J.; Freedland, K.E.; de Groot, M.; Carney, R.M.; Clouse, R.E. Depression and poor glycemic control: A meta-analytic review of the literature. *Diabetes Care* **2000**, *23*, 934–942. [CrossRef] [PubMed]

337. Svenningsson, P.; Berg, L.; Matthews, D.; Ionescu, D.F.; Richards, E.M.; Niciu, M.J.; Malinger, A.; Toups, M.; Manji, H.; Trivedi, M.H.; et al. Preliminary evidence that early reduction in p11 levels in natural killer cells and monocytes predicts the likelihood of antidepressant response to chronic citalopram. *Mol. Psychiatry* **2014**, *19*, 962–964. [CrossRef]

338. Pajer, K.; Andrus, B.M.; Gardner, W.; Lourie, A.; Strange, B.; Campo, J.; Bridge, J.; Blizinsky, K.; Dennis, K.; Vedell, P.; et al. Discovery of blood transcriptomic markers for depression in animal models and pilot validation in subjects with early-onset major depression. *Transl. Psychiatry* **2012**, *2*, e101. [CrossRef]

339. Redei, E.E.; Andrus, B.M.; Kwasny, M.J.; Seok, J.; Cai, X.; Ho, J.; Mohr, D.C. Blood transcriptomic biomarkers in adult primary care patients with major depressive disorder undergoing cognitive behavioral therapy. *Transl. Psychiatry* **2014**, *4*, e442. [CrossRef]

340. Bocchio-Chiavetto, L.; Maffioletti, E.; Bettinsoli, P.; Giovannini, C.; Bignotti, S.; Tardito, D.; Corrada, D.; Milanesi, L.; Gennarelli, M. Blood microRNA changes in depressed patients during antidepressant treatment. *Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol.* **2013**, *23*, 602–611. [CrossRef]

341. Belzeaux, R.; Formisano-Tréziny, C.; Loundou, A.; Boyer, L.; Gabert, J.; Samuelian, J.-C.; Féron, F.; Naudin, J.; Ibrahim, E.C. Clinical variations modulate patterns of gene expression and define blood biomarkers in major depression. *J. Psychiatr. Res.* **2010**, *44*, 1205–1213. [CrossRef]

342. Iacob, E.; Light, K.C.; Tadler, S.C.; Weeks, H.R.; White, A.T.; Hughen, R.W.; VanHaitsma, T.A.; Bushnell, L.; Light, A.R. Dysregulation of leukocyte gene expression in women with medication-refractory depression versus healthy non-depressed controls. *BMC Psychiatry* **2013**, *13*, 273. [CrossRef]

343. Tsao, C.-W.; Lin, Y.-S.; Chen, C.-C.; Bai, C.-H.; Wu, S.-R. Cytokines and serotonin transporter in patients with major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2006**, *30*, 899–905. [CrossRef] [PubMed]

344. Capuron, L.; Ravaud, A.; Neveu, P.J.; Miller, A.H.; Maes, M.; Dantzer, R. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol. Psychiatry* **2002**, *7*, 468–473. [CrossRef] [PubMed]

345. Dantzer, R. Role of the kynurenine metabolism pathway in inflammation-induced depression—Preclinical approaches. *Curr. Top. Behav. Neurosci.* **2017**, *31*, 117–138. [CrossRef] [PubMed]

346. Ogawa, S.; Fujii, T.; Koga, N.; Hori, H.; Teraishi, T.; Hattori, K.; Noda, T.; Higuchi, T.; Motohashi, N.; Kunugi, H. Plasma L-tryptophan concentration in major depressive disorder: New data and meta-analysis. *J. Clin. Psychiatry* **2014**, *75*, e906–e915. [CrossRef] [PubMed]

347. Fernstrom, J.D.; Wurtman, R.J. Brain serotonin content: Physiological dependence on plasma tryptophan levels. *Science* **1971**, *173*, 149–152. [CrossRef]

348. Young, S.N. The effect of raising and lowering tryptophan levels on human mood and social behaviour. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2013**, *368*, 20110375. [CrossRef]

349. Kaddurah-Daouk, R.; Bogdanov, M.B.; Wikoff, W.R.; Zhu, H.; Boyle, S.H.; Churchill, E.; Wang, Z.; Rush, A.J.; Krishnan, R.R.; Pickering, E.; et al. Pharmacometabolomic mapping of early biochemical changes induced by sertraline and placebo. *Transl. Psychiatry* **2013**, *3*, e223. [CrossRef]

350. Maes, M.; Leonard, B.E.; Myint, A.M.; Kubera, M.; Verkerk, R. The new "5-HT" hypothesis of depression: Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 702–721. [CrossRef]

351. O'Connor, J.C.; André, C.; Wang, Y.; Lawson, M.A.; Szegedi, S.S.; Lestage, J.; Castanon, N.; Kelley, K.W.; Dantzer, R. Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus calmette-guerin. *J. Neurosci. Off. J. Soc. Neurosci.* **2009**, *29*, 4200–4209. [CrossRef]

352. O'Connor, J.C.; Lawson, M.A.; André, C.; Briley, E.M.; Szegedi, S.S.; Lestage, J.; Castanon, N.; Herkenham, M.; Dantzer, R.; Kelley, K.W. Induction of IDO by bacille calmette-guérin is responsible for development of murine depressive-like behavior. *J. Immunol. Baltim. Md. 1950* **2009**, *182*, 3202–3212. [CrossRef]

353. O'Connor, J.C.; Lawson, M.A.; André, C.; Moreau, M.; Lestage, J.; Castanon, N.; Kelley, K.W.; Dantzer, R. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol. Psychiatry* **2009**, *14*, 511–522. [CrossRef] [PubMed]

354. Curzon, G.; Bridges, P.K. Tryptophan metabolism in depression. *J. Neurol. Neurosurg. Psychiatry* **1970**, *33*, 698–704. [CrossRef] [PubMed]

355. Sun, Y. Indoleamine 2,3-dioxygenase—A new antioxidant enzyme. *Mater. Med. Pol. Pol. J. Med. Pharm.* **1989**, *21*, 244–250.

356. Mackay, G.M.; Forrest, C.M.; Christofides, J.; Bridel, M.A.; Mitchell, S.; Cowlard, R.; Stone, T.W.; Darlington, L.G. Kynurenine metabolites and inflammation markers in depressed patients treated with fluoxetine or counselling. *Clin. Exp. Pharm. Physiol.* **2009**, *36*, 425–435. [CrossRef] [PubMed]

357. Ogyu, K.; Kubo, K.; Noda, Y.; Iwata, Y.; Tsugawa, S.; Omura, Y.; Wada, M.; Tarumi, R.; Plitman, E.; Moriguchi, S.; et al. Kynurenine pathway in depression: A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* **2018**, *90*, 16–25. [CrossRef] [PubMed]

358. Myint, A.-M.; Kim, Y.K.; Verkerk, R.; Scharpé, S.; Steinbusch, H.; Leonard, B. Kynurenine pathway in major depression: Evidence of impaired neuroprotection. *J. Affect. Disord.* **2007**, *98*, 143–151. [CrossRef] [PubMed]

359. Guillemin, G.J.; Smythe, G.; Takikawa, O.; Brew, B.J. Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. *Glia* **2005**, *49*, 15–23. [CrossRef]

360. Kalkman, H.O.; Feuerbach, D. Antidepressant therapies inhibit inflammation and microglial M1-polarization. *Pharm. Ther.* **2016**, *163*, 82–93. [CrossRef]

361. Banasr, M.; Duman, R.S. Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. *Biol. Psychiatry* **2008**, *64*, 863–870. [CrossRef]

362. Schroeter, M.L.; Abdul-Khaliq, H.; Krebs, M.; Diefenbacher, A.; Blasig, I.E. Serum markers support disease-specific glial pathology in major depression. *J. Affect. Disord.* **2008**, *111*, 271–280. [CrossRef]

363. Loscalzo, J.; Kohane, I.; Barabasi, A.-L. Human disease classification in the postgenomic era: A complex systems approach to human pathobiology. *Mol. Syst. Biol.* **2007**, *3*, 124. [CrossRef] [PubMed]

364. Paige, L.A.; Mitchell, M.W.; Krishnan, K.R.R.; Kaddurah-Daouk, R.; Steffens, D.C. A preliminary metabolomic analysis of older adults with and without depression. *Int. J. Geriatr. Psychiatry* **2007**, *22*, 418–423. [CrossRef] [PubMed]

365. Xu, H.-B.; Fang, L.; Hu, Z.-C.; Chen, Y.-C.; Chen, J.-J.; Li, F.-F.; Lu, J.; Mu, J.; Xie, P. Potential clinical utility of plasma amino acid profiling in the detection of major depressive disorder. *Psychiatry Res.* **2012**, *200*, 1054–1057. [CrossRef] [PubMed]

366. Liu, Y.; Yieh, L.; Yang, T.; Drinkenburg, W.; Peeters, P.; Steckler, T.; Narayan, V.A.; Wittenberg, G.; Ye, J. Metabolomic biosignature differentiates melancholic depressive patients from healthy controls. *BMC Genom.* **2016**, *17*, 669. [CrossRef]

367. Steffens, D.C.; Jiang, W.; Krishnan, K.R.R.; Karoly, E.D.; Mitchell, M.W.; O'Connor, C.M.; Kaddurah-Daouk, R. Metabolomic differences in heart failure patients with and without major depression. *J. Geriatr. Psychiatry Neurol.* **2010**, *23*, 138–146. [CrossRef]

368. Zheng, P.; Wang, Y.; Chen, L.; Yang, D.; Meng, H.; Zhou, D.; Zhong, J.; Lei, Y.; Melgiri, N.D.; Xie, P. Identification and validation of urinary metabolite biomarkers for major depressive disorder. *Mol. Cell. Proteom. MCP* **2013**, *12*, 207–214. [CrossRef]

369. Zheng, P.; Chen, J.; Huang, T.; Wang, M.; Wang, Y.; Dong, M.; Huang, Y.; Zhou, L.; Xie, P. A novel urinary metabolite signature for diagnosing major depressive disorder. *J. Proteome Res.* **2013**, *12*, 5904–5911. [CrossRef]

370. Chen, J.; Bai, S.-J.; Li, W.; Zhou, C.; Zheng, P.; Fang, L.; Wang, H.; Liu, Y.; Xie, P. Urinary biomarker panel for diagnosing patients with depression and anxiety disorders. *Transl. Psychiatry* **2018**, *8*, 192. [CrossRef]

371. MacDonald, K.; Krishnan, A.; Cervenka, E.; Hu, G.; Guadagno, E.; Trakadis, Y. Biomarkers for major depressive and bipolar disorders using metabolomics: A systematic review. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **2019**, *180*, 122–137. [CrossRef]

372. Grimble, G. Glutamine, glutamate and pyroglutamate—Facts and fantasies. *Clin. Nutr.* **1993**, *12*, 66–69. [CrossRef]

373. Janowsky, D.S.; el-Yousef, M.K.; Davis, J.M.; Sekerke, H.J. A cholinergic-adrenergic hypothesis of mania and depression. *Lancet Lond. Engl.* **1972**, *2*, 632–635. [CrossRef]

374. Chen, L.-P.; Dai, H.-Y.; Dai, Z.-Z.; Xu, C.-T.; Wu, R.-H. Anterior cingulate cortex and cerebellar hemisphere neurometabolite changes in depression treatment: A 1H magnetic resonance spectroscopy study. *Psychiatry Clin. Neurosci.* **2014**, *68*, 357–364. [CrossRef] [PubMed]

375. Moffett, J.R.; Ross, B.; Arun, P.; Madhavarao, C.N.; Namboodiri, M.A.A. N-Acetylaspartate in the CNS: From neurodiagnostics to neurobiology. *Prog. Neurobiol.* **2007**, *81*, 89–131. [CrossRef] [PubMed]

376. Kaddurah-Daouk, R.; Boyle, S.H.; Matson, W.; Sharma, S.; Matson, S.; Zhu, H.; Bogdanov, M.B.; Churchill, E.; Krishnan, R.R.; Rush, A.J.; et al. Pretreatment metabotype as a predictor of response to sertraline or placebo in depressed outpatients: A proof of concept. *Transl. Psychiatry* **2011**, *1*. [CrossRef] [PubMed]

377. Itoh, K.; Chiba, T.; Takahashi, S.; Ishii, T.; Igarashi, K.; Katoh, Y.; Oyake, T.; Hayashi, N.; Satoh, K.; Hatayama, I.; et al. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 313–322. [CrossRef]

378. Mellon, S.H.; Wolkowitz, O.M.; Schonemann, M.D.; Epel, E.S.; Rosser, R.; Burke, H.B.; Mahan, L.; Reus, V.I.; Stamatiou, D.; Liew, C.-C.; et al. Alterations in leukocyte transcriptional control pathway activity associated with major depressive disorder and antidepressant treatment. *Transl. Psychiatry* **2016**, *6*, e821. [CrossRef]

379. Freland, L.; Beaulieu, J.-M. Inhibition of GSK3 by lithium, from single molecules to signaling networks. *Front. Mol. Neurosci.* **2012**, *5*, 14. [CrossRef]

380. Martins-de-Souza, D.; Guest, P.C.; Harris, L.W.; Vanattou-Saifoudine, N.; Webster, M.J.; Rahmoune, H.; Bahn, S. Identification of proteomic signatures associated with depression and psychotic depression in post-mortem brains from major depression patients. *Transl. Psychiatry* **2012**, *2*, e87. [CrossRef]

381. Cao, X.; Li, L.-P.; Wang, Q.; Wu, Q.; Hu, H.-H.; Zhang, M.; Fang, Y.-Y.; Zhang, J.; Li, S.-J.; Xiong, W.-C.; et al. Astrocyte-derived ATP modulates depressive-like behaviors. *Nat. Med.* **2013**, *19*, 773–777. [CrossRef]

382. Marsden, W.N. Synaptic plasticity in depression: Molecular, cellular and functional correlates. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2013**, *43*, 168–184. [CrossRef]

383. Fava, M.; Kendler, K.S. Major depressive disorder. *Neuron* **2000**, *28*, 335–341. [CrossRef]

384. Risch, N.; Herrell, R.; Lehner, T.; Liang, K.-Y.; Eaves, L.; Hoh, J.; Griem, A.; Kovacs, M.; Ott, J.; Merikangas, K.R. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. *JAMA* **2009**, *301*, 2462–2471. [CrossRef] [PubMed]

385. Lohoff, F.W. Overview of the genetics of major depressive disorder. *Curr. Psychiatry Rep.* **2010**, *12*, 539–546. [CrossRef] [PubMed]

386. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium; Ripke, S.; Wray, N.R.; Lewis, C.M.; Hamilton, S.P.; Weissman, M.M.; Breen, G.; Byrne, E.M.; Blackwood, D.H.R.; Boomsma, D.I.; et al. A mega-analysis of genome-wide association studies for major depressive disorder. *Mol. Psychiatry* **2013**, *18*, 497–511. [CrossRef]

387. Mullins, N.; Power, R.A.; Fisher, H.L.; Hanscombe, K.B.; Euesden, J.; Iniesta, R.; Levinson, D.F.; Weissman, M.M.; Potash, J.B.; Shi, J.; et al. Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. *Psychol. Med.* **2016**, *46*, 759–770. [CrossRef]

388. Lewis, S. Telomeres and depression. *Nat. Rev. Neurosci.* **2014**, *15*, 632. [CrossRef]

389. Lindqvist, D.; Epel, E.S.; Mellon, S.H.; Penninx, B.W.; Révész, D.; Verhoeven, J.E.; Reus, V.I.; Lin, J.; Mahan, L.; Hough, C.M.; et al. Psychiatric disorders and leukocyte telomere length: Underlying mechanisms linking mental illness with cellular aging. *Neurosci. Biobehav. Rev.* **2015**, *55*, 333–364. [CrossRef]

390. Lin, E.; Chen, P.S. Pharmacogenomics with antidepressants in the STAR*D study. *Pharmacogenomics* **2008**, *9*, 935–946. [CrossRef]

391. Benedetti, F.; Colombo, C.; Pirovano, A.; Marino, E.; Smeraldi, E. The catechol-O-methyltransferase val (108/158) met polymorphism affects antidepressant response to paroxetine in a naturalistic setting. *Psychopharmacology* **2009**, *203*, 155–160. [CrossRef]

392. Bogavac-Stanojevic, N.; Lakic, D. Biomarkers for major depressive disorder: Economic considerations. *Drug Dev. Res.* **2016**, *77*, 374–378. [CrossRef]

393. Babenko, O.; Kovalchuk, I.; Metz, G.A.S. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. *Neurosci. Biobehav. Rev.* **2015**, *48*, 70–91. [CrossRef] [PubMed]

394. Van der Doelen, R.H.A.; Arnoldussen, I.A.; Ghareh, H.; van Och, L.; Homberg, J.R.; Kozicz, T. Early life adversity and serotonin transporter gene variation interact to affect DNA methylation of the corticotropin-releasing factor gene promoter region in the adult rat brain. *Dev. Psychopathol.* **2015**, *27*, 123–135. [CrossRef] [PubMed]

395. Zheng, Y.; Fan, W.; Zhang, X.; Dong, E. Gestational stress induces depressive-like and anxiety-like phenotypes through epigenetic regulation of BDNF expression in offspring hippocampus. *Epigenetics* **2016**, *11*, 150–162. [CrossRef] [PubMed]

396. D'Addario, C.; Dell'Osso, B.; Galimberti, D.; Palazzo, M.C.; Benatti, B.; Di Francesco, A.; Scarpini, E.; Altamura, A.C.; Maccarrone, M. Epigenetic modulation of BDNF gene in patients with major depressive disorder. *Biol. Psychiatry* **2013**, *73*, e6–e7. [CrossRef] [PubMed]

397. Wulff, K.; Gatti, S.; Wettstein, J.G.; Foster, R.G. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat. Rev. Neurosci.* **2010**, *11*, 589–599. [CrossRef]

398. Karatsoreos, I.N. Links between circadian rhythms and psychiatric disease. *Front. Behav. Neurosci.* **2014**, *8*. [CrossRef]

399. Korb, A.S.; Hunter, A.M.; Cook, I.A.; Leuchter, A.F. Rostral anterior cingulate cortex theta current density and response to antidepressants and placebo in major depression. *Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.* **2009**, *120*, 1313–1319. [CrossRef]

400. Langer, S.Z.; Zarifian, E.; Briley, M.; Raisman, R.; Sechter, D. High-affinity 3H-imipramine binding: A new biological marker in depression. *Pharmacopsychiatria* **1982**, *15*, 4–10. [CrossRef]

401. Ellis, P.M.; Salmond, C. Is platelet imipramine binding reduced in depression? A meta-analysis. *Biol. Psychiatry* **1994**, *36*, 292–299. [CrossRef]

402. Carvalho, L.A.; Torre, J.P.; Papadopoulos, A.S.; Poon, L.; Juruena, M.F.; Markopoulou, K.; Cleare, A.J.; Pariante, C.M. Lack of clinical therapeutic benefit of antidepressants is associated overall activation of the inflammatory system. *J. Affect. Disord.* **2013**, *148*, 136–140. [CrossRef]

403. Chamberlain, S.R.; Cavanagh, J.; de Boer, P.; Mondelli, V.; Jones, D.N.C.; Drevets, W.C.; Cowen, P.J.; Harrison, N.A.; Pointon, L.; Pariante, C.M.; et al. Treatment-resistant depression and peripheral C-reactive protein. *Br. J. Psychiatry* **2019**, *214*, 11–19. [CrossRef] [PubMed]

404. Haroon, E.; Daguanno, A.W.; Woolwine, B.J.; Goldsmith, D.R.; Baer, W.M.; Wommack, E.C.; Felger, J.C.; Miller, A.H. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. *Psychoneuroendocrinology* **2018**, *95*, 43–49. [CrossRef] [PubMed]

405. Jani, B.D.; McLean, G.; Nicholl, B.I.; Barry, S.J.E.; Sattar, N.; Mair, F.S.; Cavanagh, J. Risk assessment and predicting outcomes in patients with depressive symptoms: A review of potential role of peripheral blood based biomarkers. *Front. Hum. Neurosci.* **2015**, *9*. [CrossRef] [PubMed]

406. Angst, J.; Gamma, A.; Benazzi, F.; Ajdacic, V.; Rössler, W. Melancholia and atypical depression in the Zurich study: Epidemiology, clinical characteristics, course, comorbidity and personality. *Acta Psychiatr. Scand. Suppl.* **2007**, 72–84. [CrossRef] [PubMed]

407. Day, C.V.A.; Williams, L.M. Finding a biosignature for melancholic depression. *Expert Rev. Neurother.* **2012**, *12*, 835–847. [CrossRef]

408. Gili, M.; Roca, M.; Armengol, S.; Asensio, D.; Garcia-Campayo, J.; Parker, G. Clinical patterns and treatment outcome in patients with melancholic, atypical and non-melancholic depressions. *PLoS ONE* **2012**, *7*, e48200. [CrossRef]

409. Bobo, W.V.; Chen, H.; Trivedi, M.H.; Stewart, J.W.; Nierenberg, A.A.; Fava, M.; Kurian, B.T.; Warden, D.; Morris, D.W.; Luther, J.F.; et al. Randomized comparison of selective serotonin reuptake inhibitor (escitalopram) monotherapy and antidepressant combination pharmacotherapy for major depressive disorder with melancholic features: A CO-MED report. *J. Affect. Disord.* **2011**, *133*, 467–476. [CrossRef]

410. Wiethoff, K.; Bauer, M.; Baghai, T.C.; Möller, H.-J.; Fisher, R.; Hollinde, D.; Kiermeir, J.; Hauth, I.; Laux, G.; Cordes, J.; et al. Prevalence and treatment outcome in anxious versus nonanxious depression: Results from the German algorithm project. *J. Clin. Psychiatry* **2010**, *71*, 1047–1054. [CrossRef]

411. Willner, P. Validity, reliability and utility of the chronic mild stress model of depression: A 10-year review and evaluation. *Psychopharmacology* **1997**, *134*, 319–329. [CrossRef]

412. Forbes, N.F.; Stewart, C.A.; Matthews, K.; Reid, I.C. Chronic mild stress and sucrose consumption: Validity as a model of depression. *Physiol. Behav.* **1996**, *60*, 1481–1484. [CrossRef]

413. Quinn, C.; Harris, A.; Kemp, A. The interdependence of subtype and severity: Contributions of clinical and neuropsychological features to melancholia and non-melancholia in an outpatient sample. *J. Int. Neuropsychol. Soc. JINS* **2012**, *18*, 361–369. [CrossRef] [PubMed]

414. Parker, G. Classifying depression: Should paradigms lost be regained? *Am. J. Psychiatry* **2000**, *157*, 1195–1203. [CrossRef] [PubMed]

415. Buoli, M.; Caldiroli, A.; Altamura, A.C. Psychiatric conditions in Parkinson disease: A comparison with classical psychiatric disorders. *J. Geriatr. Psychiatry Neurol.* **2016**, *29*, 72–91. [CrossRef] [PubMed]

416. Malhi, G.S.; Parker, G.B.; Greenwood, J. Structural and functional models of depression: From sub-types to substrates. *Acta Psychiatr. Scand.* **2005**, *111*, 94–105. [CrossRef]

417. Souery, D.; Oswald, P.; Massat, I.; Bailer, U.; Bollen, J.; Demyttenaere, K.; Kasper, S.; Lecrubier, Y.; Montgomery, S.; Serretti, A.; et al. Clinical factors associated with treatment resistance in major depressive disorder: Results from a European multicenter study. *J. Clin. Psychiatry* **2007**, *68*, 1062–1070. [CrossRef]

418. Bauer, M.; Pfennig, A.; Severus, E.; Whybrow, P.C.; Angst, J.; Möller, H.-J. World Federation of Societies of Biological Psychiatry. Task force on unipolar depressive disorders world federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders. *World J. Biol. Psychiatry Off. J. World Fed. Soc. Biol. Psychiatry* **2013**, *14*, 334–385. [CrossRef]

419. Christensen, M.C.; Munro, V. Cost per successfully treated patient for vortioxetine versus duloxetine in adults with major depressive disorder: An analysis of the complete symptoms of depression and functional outcome. *Curr. Med. Res. Opin.* **2018**, *34*, 593–600. [CrossRef]

420. Ambrée, O.; Bergink, V.; Grosse, L.; Alferink, J.; Drexhage, H.A.; Rothermundt, M.; Arolt, V.; Birkenhäger, T.K. S100B Serum levels predict treatment response in patients with melancholic depression. *Int. J. Neuropsychopharmacol.* **2015**, *19*, pyv103. [CrossRef]

421. Yoon, H.-K.; Kim, Y.-K.; Lee, H.-J.; Kwon, D.-Y.; Kim, L. Role of cytokines in atypical depression. *Nord. J. Psychiatry* **2012**, *66*, 183–188. [CrossRef]

422. Esposito, C.M.; Buoli, M. The biological face of melancholia: Are there any reliable biomarkers for this depression subtype? *J. Affect. Disord.* **2020**, *266*, 802–809. [CrossRef]

423. Lu, Y.-R.; Fu, X.-Y.; Shi, L.-G.; Jiang, Y.; Wu, J.-L.; Weng, X.-J.; Wang, Z.-P.; Wu, X.-Y.; Lin, Z.; Liu, W.-B.; et al. Decreased plasma neuroactive amino acids and increased nitric oxide levels in melancholic major depressive disorder. *BMC Psychiatry* **2014**, *14*, 123. [CrossRef] [PubMed]

424. Gold, P.W.; Chrousos, G.P. Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs. low CRH/NE states. *Mol. Psychiatry* **2002**, *7*, 254–275. [CrossRef] [PubMed]

425. Taylor, M.A.; Fink, M. Restoring melancholia in the classification of mood disorders. *J. Affect. Disord.* **2008**, *105*, 1–14. [CrossRef] [PubMed]

426. Maes, M.; Bosmans, E.; Suy, E.; Vandervorst, C.; DeJonckheere, C.; Raus, J. Depression-related disturbances in mitogen-induced lymphocyte responses and interleukin-1β and soluble interleukin-2 receptor production. *Acta Psychiatr. Scand.* **1991**, *84*, 379–386. [CrossRef] [PubMed]

427. Maes, M.; Lambrechts, J.; Bosmans, E.; Jacobs, J.; Suy, E.; Vandervorst, C.; de Jonckheere, C.; Minner, B.; Raus, J. Evidence for a systemic immune activation during depression: Results of leukocyte enumeration by flow cytometry in conjunction with monoclonal antibody staining. *Psychol. Med.* **1992**, *22*, 45–53. [CrossRef] [PubMed]

428. Maes, M.; Scharpé, S.; Meltzer, H.Y.; Okayli, G.; Bosmans, E.; D'Hondt, P.; Vanden Bossche, B.; Cosyns, P. Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: Further evidence for an immune response. *Psychiatry Res.* **1994**, *54*, 143–160. [CrossRef]

429. Rothermundt, M.; Arolt, V.; Fenker, J.; Gutbrodt, H.; Peters, M.; Kirchner, H. Different immune patterns in melancholic and non-melancholic major depression. *Eur. Arch. Psychiatry Clin. Neurosci.* **2001**, *251*, 90–97. [CrossRef]

430. Erdem, M.; Celik, C.; Cayci, T.; Ozdemir, B.; Kurt, Y.G.; Akgul, E.O.; Yaman, H.; Balikci, A.; Uzun, O. Serum haptoglobin levels in patients with melancholic and nonmelancholic major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2011**, *35*, 944–947. [CrossRef]

431. Dunjic-Kostic, B.; Ivkovic, M.; Radonjic, N.V.; Petronijevic, N.D.; Pantovic, M.; Damjanovic, A.; Poznanovic, S.T.; Jovanovic, A.; Nikolic, T.; Jasovic-Gasic, M. Melancholic and atypical major depression—Connection between cytokines, psychopathology and treatment. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2013**, *43*, 1–6. [CrossRef]

432. Maes, M.; Scharpé, S.; Meltzer, H.Y.; Suy, E.; Cosyns, P.; Calabrese, J. Lower angiotensin I converting enzyme activity in melancholic subjects: A pilot study. *Biol. Psychiatry* **1992**, *32*, 621–624. [CrossRef]

433. Antonijevic, I.; Antonijevic, I. HPA axis and sleep: Identifying subtypes of major depression. *Stress* **2008**, *11*, 15–27. [CrossRef] [PubMed]

434. Cizza, G.; Ronsaville, D.S.; Kleitz, H.; Eskandari, F.; Mistry, S.; Torvik, S.; Sonbolian, N.; Reynolds, J.C.; Blackman, M.R.; Gold, P.W.; et al. Clinical subtypes of depression are associated with specific metabolic parameters and circadian endocrine profiles in women: The power study. *PLoS ONE* **2012**, *7*, e28912. [CrossRef] [PubMed]

435. Capuron, L.; Lasselin, J.; Castanon, N. Role of adiposity-driven inflammation in depressive morbidity. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* **2017**, *42*, 115–128. [CrossRef] [PubMed]

436. Scarr, E.; Millan, M.J.; Bahn, S.; Bertolino, A.; Turck, C.W.; Kapur, S.; Möller, H.-J.; Dean, B. Biomarkers for psychiatry: The journey from fantasy to fact, a report of the 2013 CINP think tank. *Int. J. Neuropsychopharmacol.* **2015**, *18*, pyv042. [CrossRef] [PubMed]

437. Trivedi, M.H.; McGrath, P.J.; Fava, M.; Parsey, R.V.; Kurian, B.T.; Phillips, M.L.; Oquendo, M.A.; Bruder, G.; Pizzagalli, D.; Toups, M.; et al. Establishing moderators and biosignatures of antidepressant response in clinical care (EMBARC): Rationale and design. *J. Psychiatr. Res.* **2016**, *78*, 11–23. [CrossRef]

438. Strawbridge, R.; Young, A.H.; Cleare, A.J. Biomarkers for depression: Recent insights, current challenges and future prospects. *Neuropsychiatr. Dis. Treat.* **2017**, *13*, 1245–1262. [CrossRef]

439. Andrews, G.; Brugha, T.; Thase, M.E.; Duffy, F.F.; Rucci, P.; Slade, T. Dimensionality and the category of major depressive episode. *Int. J. Methods Psychiatr. Res.* **2007**, *16*, S41–S51. [CrossRef]

440. Waszkiewicz, N. Mentally sick or not—(Bio)markers of psychiatric disorders needed. *J. Clin. Med.* **2020**, *9*, 2375. [CrossRef]

441. Pinto, J.V.; Moulin, T.C.; Amaral, O.B. On the transdiagnostic nature of peripheral biomarkers in major psychiatric disorders: A systematic review. *Neurosci. Biobehav. Rev.* **2017**, *83*, 97–108. [CrossRef]

442. Woody, M.L.; Gibb, B.E. Integrating NIMH research domain criteria (RDoC) into depression research. *Curr. Opin. Psychol.* **2015**, *4*, 6–12. [CrossRef]

443. Carvalho, A.F.; Köhler, C.A.; Brunoni, A.R.; Miskowiak, K.W.; Herrmann, N.; Lanctôt, K.L.; Hyphantis, T.N.; Quevedo, J.; Fernandes, B.S.; Berk, M. Bias in peripheral depression biomarkers. *Psychother. Psychosom.* **2016**, *85*, 81–90. [CrossRef]

444. Feczko, E.; Miranda-Dominguez, O.; Marr, M.; Graham, A.M.; Nigg, J.T.; Fair, D.A. The heterogeneity problem: Approaches to identify psychiatric subtypes. *Trends Cogn. Sci.* **2019**, *23*, 584–601. [CrossRef] [PubMed]

445. Beijers, L.; Wardenaar, K.J.; Bosker, F.J.; Lamers, F.; van Grootheest, G.; de Boer, M.K.; Penninx, B.W.J.H.; Schoevers, R.A. Biomarker-based subtyping of depression and anxiety disorders using latent class analysis. A NESDA study. *Psychol. Med.* **2019**, *49*, 617–627. [CrossRef] [PubMed]

446. Alcocer-Gómez, E.; de Miguel, M.; Casas-Barquero, N.; Núñez-Vasco, J.; Sánchez-Alcazar, J.A.; Fernández-Rodríguez, A.; Cordero, M.D. NLRP3 inflammasome is activated in mononuclear blood cells from patients with major depressive disorder. *Brain Behav. Immun.* **2014**, *36*, 111–117. [CrossRef] [PubMed]

447. Hayashi-Takagi, A.; Vawter, M.P.; Iwamoto, K. Peripheral biomarkers revisited: Integrative profiling of peripheral samples for psychiatric research. *Biol. Psychiatry* **2014**, *75*, 920–928. [CrossRef] [PubMed]

Article

Urine 3-Nitrotyrosine and Serum HDL as Potential Biomarkers of Depression

Aleksander Nobis [1,*], Daniel Zalewski [1], Eliza Samaryn [1], Mateusz Maciejczyk [2], Anna Zalewska [3] and Napoleon Waszkiewicz [1]

[1] Department of Psychiatry, Medical University of Białystok, ul. Wołodyjowskiego 2, 15-369 Białystok, Poland
[2] Department of Hygiene, Epidemiology, and Ergonomics, Medical University of Białystok, 15-089 Białystok, Poland
[3] Department of Restorative Dentistry, Medical University of Białystok, ul. M. Skłodowskiej-Curie 24A, 15-276 Białystok, Poland
* Correspondence: aleksander.nobis@sd.umb.edu.pl

Abstract: Depression (MDD) is a leading psychiatric entity worldwide, with a high impact on individual life and public health. In recent years, efforts have been made to elucidate its biological underpinnings. MDD biomarker research provides promise for a better understanding of the biochemical processes involved in its pathogenesis. Oxidative and nitrosative stress (O&NS) and lipid disturbances are reported as major factors favoring the occurrence of depression. A total of 29 patients with MDD and 30 healthy volunteers were examined using the Hamilton Depression Scale (HAM-D), the Hamilton Anxiety Scale (HAM-A), and the Beck Depression Inventory (BDI). Blood and urine were collected to search for potential MDD biomarkers. O&NS parameters and β-amyloid were assessed in the urine, while cholesterol fractions were assessed in the blood. The group of depressed patients was characterized by higher concentrations of urine superoxide dismutase (SOD), 3-nitrotyrosine (3-NT), catalase (CAT), reduced glutathione (GSH), tryptophan (TRY), and serum triglycerides (TGA), along with lower levels of serum high-density lipoprotein (HDL). Elevated urine 3-NT and decreased serum HDL, considered together, were found to have the greatest potential as markers of depression. The study supports the importance of oxidative stress and cholesterol disturbances in MDD. Further research is required to assess their clinical usefulness as markers.

Keywords: 3-nitrotyrosine; oxidative stress; HDL; biomarker; marker; depression; MDD; urine; cholesterol; β-amyloid

1. Introduction

Depression (MDD) is a leading psychiatric entity, affecting 350 million people worldwide, i.e., 5% of the global population [1]. It is characterized by a high suicide rate and a high number of disability-adjusted life years, and it has a substantial impact on a patient's quality of life [2]. MDD is clinically characterized by lowered mood, lack of energy, anhedonia, sleep and appetite disturbances, problems with concentration, decreased libido, and suicidal thoughts. Nevertheless, the clinical image of MDD may vary considerably from person to person, so much so that several subtypes of depression have been described. MDD is a complex and heterogeneous disorder with multiple psychological, social, and biological factors involved in its etiopathogenesis. Genetic predisposition, monoamine deficiency, stress axis dysregulation, and pro-inflammatory state are among the major biological factors enhancing depression development. Oxidative and nitrosative stress (O&NS), closely interrelated with the inflammatory processes, are also reported as pivotal biological factors involved in depression [3]. Oxidative stress is a persistent imbalance between the antioxidant defense system and oxidative damage, caused by reactive oxygen species (ROS), which are a side product of the mitochondrial oxidative chain. The main ROS include hydrogen peroxide, hydroxy radical, and superoxide anion [4]. Interestingly, the

brain is particularly vulnerable to oxidative damage due to high oxygen consumption per weight unit, high concentration of unsaturated fatty acids, and oxidative defense system paucity. Nitrosative stress is a measure of the detrimental effect exerted on body cells by reactive nitrogen species (RNS). Examples of RNS are nitric oxide and peroxynitrite. ROS/RNS were found in the brain tissue of depressed patients in a post-mortem study [5]. Under physiological conditions, ROS/RNS are neutralized by several anti-oxidant defense pathways, including ROS/RNS scavenging (e.g., glutathione) or enzymatic deactivation (e.g., superoxide dismutase, glutathione peroxidase, and catalase). There are also ways through which oxidative stress favors anti-oxidant processes activation (e.g., an increase in Nrf-2 levels, which itself promotes antioxidant genes transcription) [6]. The interplay between pro- and antioxidant systems in depression has been described in detail by Maes and Carvalho [7]. When not efficiently counterbalanced by anti-oxidant systems, ROS/RNS damage cellular macromolecules, such as proteins, lipids, and DNA, leading to a formation of so-called neo-epitopes, which increase the autoimmune response. Such damages have been proved in MDD [8]. There is evidence that MDD is characterized by a neurodegenerative process [9], and O&NS pathways, when activated, favor neurodegeneration through different mechanisms, including direct ROS/RNS detrimental effect, enhanced neuroinflammation, and neurotoxic effects of by-products of the ROS-activated kynurenine pathway—quinolinic acid (QA) and 3-hydroxykynurenine (3-HKN) [10]. Interestingly, the activation of indoleamine 2,3-dioxygenase (IDO)—an enzyme of the kynurenine pathway— is likely the means through which inflammation induces depression [11]. Oxidative stress and neurodegeneration are closely interrelated. Oxidative stress is involved in the etiology of neurodegenerative disorders such as Alzheimer's disease (AD). In AD, redox active metal ions (e.g., copper, iron, or zinc) aggregate with β-amyloid peptide—the hallmark of AD. When bound, they can promote ROS production and enhance the oxidative damage of the β-amyloid peptide itself, as well as other surrounding molecules, such as lipids or proteins [12,13]. Interestingly, MDD is known to be a prodrome and a risk factor of AD. Moreover, there is a certain overlap in behavioral signs of MDD and AD [14]. That is why β-amyloid was investigated as potentially altered in MDD, especially in older patients, with conflicting results [15,16]. In the majority of PET studies, higher levels of cortical β-amyloid deposition were found in elderly depressive patients [17–19], while contradictory results have also been reported [20,21].

The psychiatric diagnostic process, unlike the process in many other medical fields, remains mainly symptom-based. Today's psychiatry research, tending toward more objective disease diagnosis and more personalized treatment, focuses on disease biomarkers. The better understanding of underlying pathophysiological processes may lead to a more accurate diagnosis and better-tailored treatment. An increasing body of evidence suggests the existence of several biochemical markers of MDD, able to differentiate between depressive patients and the healthy population [22,23]. Some of them have the potential to monitor treatment response or to predict the increased risk of depression incidence [24]. Oxidative stress can be evidenced by the presence of oxidative stress biomarkers, which may be found in any body fluid. The majority of MDD biomarker studies focus on blood biomarkers. For example, the umbrella meta-analysis of Carvalho et al. [25] points at some promising biomarkers of depression: interleukin-6, C-reactive protein, tumor necrosis factor-α, malondialdehyde, F2-isoprostanes, glutamate, total cholesterol, brain-derived neurotrophic factor, fibroblast growth factor-2, and insulin-like growth factor-1. Urine biomarkers are an interesting alternative to those of the blood, as urine collection is easy and non-invasive, and urine biomarkers concentrations may at least partially reflect their concentration in the blood. Urinary MDD biomarkers have also been assessed in some studies. For example, Chen et al. [23] discovered a metabolomic biomarker panel for diagnosing MDD consisting of four metabolites: aminomalonic acid, N-methylnicotinamide, hippuric acid, and azelaic acid. Van Buel et al. [26] found a set of 9 serum and 8 urine biomarkers correlating with depression.

This study aimed to assess urine oxidative stress parameters and β-amyloid concentration in the group of patients with MDD diagnosis in comparison to the healthy volunteers group to find out if they are associated with MDD and if any of them could potentially serve as MDD biomarkers.

2. Materials and Methods

2.1. Study Population

The study was conducted in the Department of Psychiatry at the Medical University of Białystok. Study participants were recruited from inpatients hospitalized with the diagnosis of unipolar depression between December 2021 and July 2022 in the Dr. Stanisław Deresz Independent Public Psychiatric Health Care Centre in Choroszcz, Poland. A total of 46 patients were eligible to participate in the study, and 17 of them eventually did not meet the inclusion criteria for one of the following reasons: lack of consent, or considerable psychiatric or somatic comorbidity. A total of 29 patients (11 men, 18 women), aged 18–65, were recruited into the study. The mean age was 43.3 years. All patients were Polish, and of Caucasian race. In the study group, there were 4 (13.8%) patients presenting with their first MDD episode and 25 (86.2%) presenting with a subsequent episode. Pregnant and breastfeeding women, and patients with obesity, diabetes, and inflammatory, autoimmune, and endocrine diseases, were excluded. None of the patients were drug-naïve at the recruitment. They received drugs from SSRI or SNRI groups or vortioxetine. The control group was recruited from among healthy volunteers, selected by sex and age to match those in the study group. The control group consisted of 30 people (10 men, 20 women), with a mean age of 41.8 years. The study design was accepted by the Ethics Committee of the Medical University of Białystok (permission: RI-002/582/2019) and was carried out in accordance with the Guidelines for Good Clinical Practice and the Helsinki Declaration. All study participants signed informed consent forms.

2.2. Study Design

The diagnosis of depression (i.e., depressive episode or recurrent depressive disorder) was based on ICD-11 criteria and confirmed by an experienced psychiatrist (N.W.). The MINI psychiatric interview was used in order to exclude other potential psychiatric entities [27]. Patients qualified in this way were then assessed with the use of the Beck Depression Inventory (BDI) [28], the Hamilton Depression Scale (HAM-D) [29], and the Hamilton Anxiety Scale (HAM-A) [30]. The persistence of depression was measured as the number of years since the beginning of the first depressive episode.

A blood analysis (complete blood count, potassium, sodium, creatinine, AlAT, AspAT, CRP, TSH, total cholesterol, LDL, HDL) was performed for each study participant before inclusion into the study in order to assess the general health of each individual. Blood analyses were performed on the Cobas Integra 400+ analyzer (Roche), using the immuno-turbidimetric method for CRP determinations, and the enzymatic-colorimetric method for total cholesterol and HDL determinations. The LDL concentration was calculated using the Friedewald formula.

Urine samples were collected from the midstream of the first-morning urine and centrifuged at $1300 \times g$ for 10 min at 4 °C. (MPW 351, MPW Med. Instruments, Warsaw, Poland). The supernatant was collected, frozen, and stored at −80 °C in Eppendorf tubes until the biochemical analysis was performed.

2.3. Biochemical Procedures

All samples were then simultaneously tested. The following parameters were assessed: Total antioxidant capacity (TAC), catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), reduced glutathione (GSH), total oxidant status (TOS), 3-nitrotyrosine (3-NT), advanced glycoxidation end products (AGEs), advanced oxidation protein products (AOPP), N-formylkynurenine (NFKN), kynurenine (KN), tryptophan (TRY), and β-amyloid.

All reagents for the biochemical assays were obtained from Sigma-Aldrich (Saint Louis, MO, USA). The list of reagent catalog numbers is listed in the Supplementary Materials. The fluorescence/absorbance was measured using an Infinite M200 PRO Multimode Microplate Reader, Tecan (Tecan Group Ltd., Männedorf, Switzerland). All determinations were standardized to 1 mg of total protein.

2.3.1. Anti-Oxidant Defense Systems Assays

Catalase (CAT) activity was assessed spectrophotometrically by measuring the decomposition rate of hydrogen peroxide. The absorbance was measured at 240 nm [31]. It was assumed that 1 unit of CAT decomposes 1 mmol hydrogen peroxide per 1 minute.

Superoxide dismutase-1 (SOD) activity was assayed spectrophotometrically by measuring the inhibition of adrenaline oxidation to adrenochrome at 480 nm [32]. A quantity of 1 unit of SOD activity was defined as a quantity of enzyme necessary to inhibit the oxidation of adrenaline by 50%.

Glutathione peroxidase (GPx) activity was assessed spectrophotometrically in the presence of NADPH and glutathione reductase, based on the reduction of organic peroxides. The absorbance was estimated at 340 nm [33]. A quantity of 1 unit of GPx activity was defined as catalyzing the oxidation of 1 μmol of NADPH per 1 minute.

Reduced glutathione (GSH) concentration was assessed spectrophotometrically based on the reaction with 5,5′-dithiobis-2-nitrobenzoic acid (DTNB). The absorbance of the resulting complex was estimated at 412 nm [34]. The standard curve for GSH (0–50 umol/L) was used.

Total antioxidant capacity (TAC) levels were estimated spectrophotometrically based on the reaction with 2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid radical cation (ABTS*+) [35]. Absorbance changes were measured at 660 nm. TAC levels were calculated with the use of the calibration curve for 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox; 0–3 mmol/L).

2.3.2. Oxidative and Nitrosative Damage Assays

The content of advanced oxidation protein product (AOPP) was estimated spectrophotometrically at 340 nm with the use of the iodine ion by measuring its oxidative capacity. For AOPP assessment, urine samples were diluted 1:50 (v/v) in phosphate-buffered saline, pH 7.2 [36]. The concentration of AOPP was calculated from the standard curve for chloramine T (0–100 umol/L).

The presence of advanced glycation end-products (AGE) was assessed fluorometrically by measuring AGE-specific fluorescence at 350 nm/440 nm. For AGE assessment, urine samples were diluted 1:50 (v/v) in phosphate-buffered saline, pH 7.2 [36].

For KN, NFKN, TRY, and 3-NT determinations, urine samples were diluted (1:10, v/v) in 0.1 M H_2SO_4. Fluorescence was analyzed at 365/480, 325/434, 95/340, and 330/415 nm, respectively, [37], and all results were normalized to a fluorescence of 0.1 mg/mL quinine sulfate (in 0.1 M H_2SO_4) [38].

The level of TOS was determined colorimetrically based on the oxidation of Fe^{2+} to Fe^{3+} ions in the presence of the oxidants in the sample [35]. The absorbance was measured bichromatically at 560/800 nm. The TOS level was calculated from the standard curve for H_2O_2 (0–200 umol/L).

The content of total protein in the samples was estimated by the bicinchoninic acid (BCA) method [39] using the commercial kit-Thermo Scientific Pierce BCA Protein Assay (Rockford, IL, USA), in accordance with the manufacturer's instructions.

The formation of beta-amyloid was evaluated by adding 10 uL of Thioflavin T to 90 uL of the urine sample. Thioflavin T fluorescence was measured at 385/485 nm [40].

2.4. Statistical Analysis

The significance level of statistical tests in the analysis was set at α = 0.05. Testing of variables on a continuous scale was performed using the Shapiro–Wilk test.

Two types of tests were used: parametric (for normally distributed variables) and nonparametric (for nonnormally distributed variables).

For normally distributed variables, the distribution measures of central tendency were given in terms of *M (SD)* and *Mdn (Q1–Q3)* for non-normally distributed variables.

The Mann–Whitney test was used to compare the means of two independent groups with nonnormal distributions. The effect size measure was estimated using the $\hat{r}_{biserial}^{rank}$. Interpretation of the effect size was based on Funder's convention [41].

The Welch's *t*-test was used to compare the means of two independent groups with normal distribution. The effect size was estimated using the $\hat{g}_{Hedges}$. Interpretation of the $\hat{g}_{Hedges}$ effect size was based on the Cohen convention [42].

The relationships between the two nominal variables were estimated using Pearson's Chi-square test and Fisher's exact test. A measure of the strength of the relationship, phi (φ), was calculated in the case of *df* = 1 and Cramer's *V,* in the case of *df* > 1.

In the case of test significance under the condition *df* > 1, equality between pairs of groups was estimated by a post hoc test using the "*BH*" method (also known as "fdr"), which controls for false discovery rate, i.e., the expected proportion of false discoveries among the rejected hypotheses [43]. The effect size of the test was also interpreted according to the Funder's convention.

The correlation of two independent variables on a continuous or quotient scale, corresponding to the assumptions of normality with *n* > 30, was calculated using Pearson's method [44], r_p. The test statistic followed a t-distribution, with (x-2) degrees of freedom.

For non-normal distributions or in the case of a small sample size ($n \leq 30$), the Spearman method was used. The *p* values were calculated using the asymptotic *t* approximation.

The multivariate effect analysis of the selected clinical parameters on the factor depression was studied with the logistic regression model, based on a generalized linear model. The iterative weighted least squares (IWLS) method was used to fit the model. The description of the error distribution and the joint function was designed based on Gaussian family objects.

The logit of the unknown probability of depression p_i was modeled as a linear function of predictors X_i based on formula (1):

$$logit(p_i) = ln(\frac{p_i}{1-p_i}) = \beta 0 + \beta_1 \cdot x_{1,i} + \ldots + \beta_k \cdot x_{k,i} \qquad (1)$$

where the observed values *Yi~binomial*, with $p = p_i$ for a given x_i and $n = k$ for binary responses.

Coefficients β_j ($j = 1, \ldots k$) were estimated using the maximum likelihood method.

The interpretation of the parameter β_j was the additive effect that a unit change in the *j* variable has on the odds ratio, defined according to Equation (2):

$$OR_{A \times B} = \frac{S(A)}{S(B)} = \frac{\frac{P(A)}{1-P(A)}}{\frac{P(B)}{1-P(B)}} = \frac{P(A) \times (1 - P(B))}{P(B) \times (1 - P(A))} \qquad (2)$$

where *A, B*—study groups, *P*—probability of occurrence of depression in a group, and *S*—chance of occurrence of depression in a group [45].

The form of the implemented regression model is expressed by Equation (3):

$$p_i = \frac{1}{1 + e^{-(\beta 0 + \beta 1 \times 1, i + \ldots + \beta k \times k, i)}} \qquad (3)$$

Standardized parameters were obtained by fitting the model on a standardized version of the dataset. The 95% confidence intervals (*CIs*) and the *p*-values were computed using a Wald *z*-distribution approximation.

Analyses were conducted using the R Statistical language (version 4.1.1) [46] on Windows 10 Pro 64 bit (build 19044), using the packages effectsize (version 0.7.0) [47], car

(version 3.0.11) [48], Hmisc (version 4.7.0) [49], ggeffects (version 1.1.1) [50], sjPlot (version 2.8.10) [51], report (version 0.5.1.3) [52], rcompanion (version 2.4.15) [53], psych (version 2.1.6) [54], and ggplot2 (version 3.3.5) [55].

3. Results

Analysis of socio-demographic data revealed no statistically significant differences in age, gender, and BMI between the study and control groups. In the study group, there were 18 (62.1%) nonsmokers, 5 (17.2%) patients who smoked less than 1 pack per day, and 6 (20.7%) who smoked more than 1 pack per day. In the control group, the distribution of patients in terms smoking was correspondingly 27 (90%), 3 (10%), and 0 (0%).

The application of an independence test showed a significant dependence between the factors group and smoking, with a large effect size, $df = 2$, $V = 0.38$, $p = 0.010$.

A post hoc test revealed a significantly greater proportion of patients who smoked more than 1 pack per day and a lower proportion of nonsmokers in the study group compared with the control group ($p_{adj} = 0.007$, $V = 0.39$).

3.1. Analysis of Differences in Clinical Data between the Groups

The analyzed clinical characteristics are presented in Table 1. The number of observations *n* reflects the real number of analyses performed.

Table 1. From the data in Table 1, there were significant differences in all questionnaire scores and in seven biochemical parameters between the study and control groups. The group of depressed patients was characterized by higher mean questionnaire scores, higher mean concentrations of serum TGA and urine SOD, 3-NT, CAT, GSH, and TRY levels, and lower serum HDL concentrations. All significant differences were characterized by large effect sizes.

	Variable	Study Group		Control Group		*p*
		n	$\hat{\mu}_{treatment}$	*n*	$\hat{\mu}_{control}$	
		Questionnaire scores				
	HAM-D score	29	24.1 (7.1)	30	0.33 (0.7)	<0.001
	Beck score	29	31.9 (11.7)	30	4.3 (4.0)	<0.001
	HAM-A score	29	20.0 (14.0–26.0)	30	0.0 (0–0)	<0.001
Material		Clinical parameters				
	Cholesterol, mg/dL	22	175.1 (45.2)	30	180.8 (36.0)	0.630
	HDL, mg/dL	22	50.1 (11.4)	30	60.1 (13.1)	0.005
serum	TGA, mg/dL	22	105.0 (77.0–137.0)	30	71.0 (56.3–100.8)	0.020
	LDL, mg/dL	22	94.5 (74.3–133.0)	30	98.5 (84.0–116.0)	0.910
	CRP, mg/L	28	1.6 (2.6)	30	1.3 (1.6)	0.550
	SOD, mU/mg protein	26	2.2 (1.1)	29	1.5 (0.8)	0.007
	3-NT, nmol/mg protein	26	0.3 (0.2 -0.3)	29	0.2 (0.2 -0.2)	0.001
	AGE, AFU/mg protein	26	60.2 (45.9–74.9)	29	56.6 (41.0–77.4)	0.550
	Amyloid, AFU/mg protein	26	9.1 (7.9–10.5)	29	7.9 (6.6–9.7)	0.080
	AOPP, nmol/mg protein	26	37.8 (32.1–42.2)	29	32.9 (28.3–35.9)	0.054
	CAT, nmol H_2O_2/min/mg protein	26	1.0 (0.9–1.3)	29	0.9 (0.8–1.1)	0.010
	GSH, ng/mg protein	26	1.4 (1.3 –1.6)	29	1.2 (1.0–1.5)	0.040
urine	KN, AFU/mg protein	26	50.6 (34.0–62.2)	29	36.5 (30.9–50.2)	0.090
	NFKN, AFU/mg protein	26	25.9 (18.3–34.6)	29	22.1 (17.2–29.1)	0.260
	GPx, mU/mg protein	26	1.1 (1.0–1.6)	29	1.0 (0.8–1.3)	0.070
	TAC, Trolox umol/mg protein	26	2.2 (1.9–3.0)	29	1.9 (1.6–2.5)	0.130
	TOS, nmol/mg protein	26	20.9 (14.8–25.7)	29	15.4 (10.7–23.4)	0.060
	TRY, AFU/mg protein	26	10.7 (9.2–12.9)	29	7.5 (5.9–9.3)	0.001

3.2. Analysis of the Relationship between Clinical Parameters, Questionnaire Scores, and Duration of Disease Progression

The results of the analysis of the associations of 18 biochemical parameters with the questionnaire scores and the disease duration factor are shown in Table 2.

Table 2. HAM-A, HAM-D, and Beck questionnaire scores and the disease duration factor showed significant associations with serum HDL and TGA and urine SOD, 3-NT, CAT, and TRY concentrations. Urine GSH correlated with the HAM-A score. All significant correlations were characterized by large effect sizes. There was a negative correlation with HDL—an increase in questionnaire scores/duration of disease persistence correlated with a decrease in HDL levels. An additive relationship was found with other parameters—an increase in questionnaire scores/duration of disease persistence correlated with an increase in TGA, SOD, 3-NT, CAT, TRY, and GSH levels. The factor that nearly all questionnaire scores correlated with the same parameters is explained by the fact that the questionnaire scores were highly correlated among themselves ($r \geq 0.80$).

Parameter	HAM-D Score			BDI Score			HAM-A Score			Persistence of Depression		
	n_{pairs}	$r_p\ (\rho)$	p	n_{pairs}	$r_p\ (\rho)$	p	n_{pairs}	ρ	p	n_{pairs}	ρ	p
Cholesterol, mg/dL	52	−0.03	0.840	52	−0.02	0.891	52	−0.15	0.285	52	−0.02	0.901
HDL, mg/dL	52	−0.33	0.017	52	−0.28	0.042	52	−0.41	0.002	52	−0.35	0.011
TGA, mg/dL	52	0.43	0.002	52	0.37	0.007	52	0.40	0.004	52	0.31	0.023
LDL, mg/dL	52	0.00	0.982	52	0.06	0.682	52	−0.05	0.734	52	0.09	0.544
CRP, mg/L	58	0.18	0.176	58	0.17	0.213	58	−0.09	0.512	58	−0.02	0.859
SOD, mU/mg protein	55	0.33	0.013	55	0.39	0.003	55	0.38	0.004	55	0.40	0.003
3-NT, nmol/mg protein	55	0.37	0.005	55	0.33	0.014	55	0.39	0.004	55	0.40	0.002
AGE, AFU/mg protein	55	0.00	0.963	55	0.02	0.893	55	0.11	0.445	55	0.03	0.802
Amyloid, AFU/mg protein	55	0.22	0.108	55	0.22	0.106	55	0.21	0.117	55	0.26	0.059
AOPP, nmol/mg protein	55	0.22	0.114	55	0.13	0.343	55	0.20	0.140	55	0.21	0.125
CAT, nmol H_2O_2/min/mg protein	55	0.27	0.044	55	0.30	0.027	55	0.30	0.028	55	0.30	0.024
GSH, ng/mg protein	55	0.17	0.202	55	0.21	0.119	55	0.27	0.043	55	0.27	0.051
KN, AFU/mg protein	55	0.21	0.189	55	0.17	0.203	55	0.21	0.123	55	0.18	0.193
NFKN, AFU/mg protein	55	0.18	0.193	55	0.14	0.307	55	0.18	0.179	55	0.11	0.437
PX, mU/mg protein	55	0.21	0.133	55	0.26	0.056	55	0.20	0.139	55	0.20	0.134
TAC, Trolox umol/mg protein	55	0.17	0.218	55	0.20	0.134	55	0.20	0.144	55	0.20	0.146
TOS, nmol/mg protein	55	0.19	0.158	55	0.27	0.044	55	0.19	0.174	55	0.20	0.141
TRY, AFU/mg protein	55	0.39	0.003	55	0.40	0.002	55	0.39	0.003	55	0.39	0.002

3.3. Multivariate Analysis Effect of Clinical Parameters on the Depression Factor

A list of seven predictors (HDL, TGA, SOD, 3-NT, GSH, CAT, TRY) was selected for the model based on the significance of differences within these variables between groups. In addition, the same predictors showed significant associations with the questionnaire scores and the duration of depression.

The model fitted with all predictors was characterized by a large variation in inflation factors (vif > 5.0) resulting from high correlations between the parameters TRY vs. SOD (0.87), TRY vs. CAT (0.86), and SOD vs. CAT (0.84). After the elimination of the CAT and TRY parameters, the fitted model had no collinearity (vif < 2.0), so the final model included five clinical parameters: HDL, TGA, SOD, 3-NT, GSH.

A logistic model was fitted to predict depression (binary variable, 1–for study group, 0–for control group.) with HDL, TGA, SOD, 3-NT and GSH (formula: depression~HDL + TGA + SOD + 3-NT + GSH).

The explanatory power of the model was considerable ($R^2_{Tjur's} = 0.37$). The model's intercept, corresponding to HDL = 0 mg/dl, TGA = 0 mg/dl, SOD = 0, mU/mg protein, 3-NT = 0 nmol/mg protein, and GSH = 0 was -2.53 (95% CI [−7.94, 2.61], $p = 0.337$).

The regression coefficients converted to the scale of OR are presented in Table 3.

The transformation of the regression coefficients and their plotting on the original probability scale are shown in Figure 1.

The estimated marginal medians (predicted values) for the response variable for significant predictors are presented in Table 4.

Table 3. From the data in Table 3, it is shown that the parameters TGA, SOD, and GSH had no significant effects on the depression factor. A 1.00 mg/dl increase in the HDL parameter decreased the log odds ratios of depression by 0.07—provided the other predictors were controlled for—as shown here and below. Increasing parameter 3 NT by 1.00 nmol/mg protein increased the log odds ratios of depression by 15.52.

Material	Predictors	Depression			
		log(OR)	*SE*	*z*	*p*
serum	(Intercept)	−2.53	2.63	−0.960	0.337
	HDL	−0.07	0.03	−2.03	0.042
	TGA	0.01	0.01	0.89	0.374
urine	SOD	0.75	0.48	1.57	0.117
	3-NT	15.52	7.55	2.06	0.040
	GSH	0.12	0.33	0.37	0.708
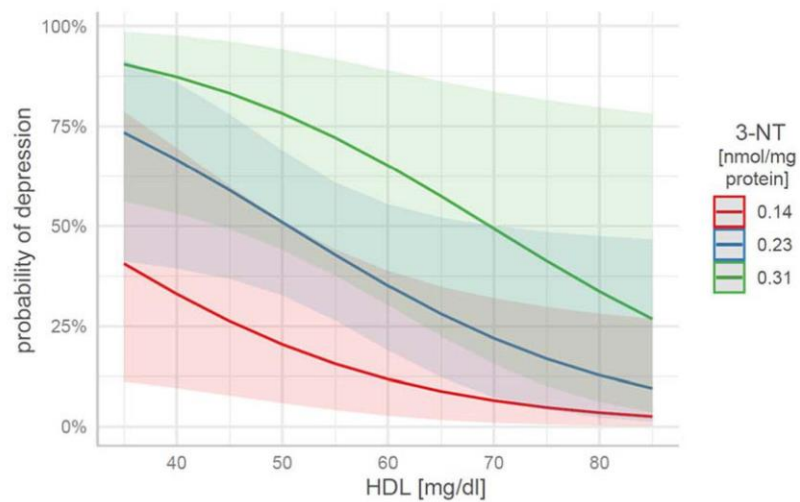
Figure 1. Expected probabilities of depression as a function of the HDL and 3-NT parameters, in the case of 3-NT for values of *M* (0.23) and within one standard deviation, 0.14 (*M*−1*SD*), 0.31 (*M*+1*SD*).

Table 4. From the data in Figure 1 and Table 4, patients with HDL < 40 mg/dl and 3-NT > 0.3 nmol/mg protein were more likely to be depressed, whereas patients with HDL > 80 mg/dl and 3-NH < 0.15 nmol/mg protein were less likely to be depressed.

HDL	3-NT	Depression Probability	95% CI ll	95% CI ul
35	0.14	0.41	0.11	0.79
35	0.23	0.73	0.41	0.92
35	0.31	0.91	0.56	0.99
60	0.14	0.11	0.03	0.39
60	0.23	0.35	0.19	0.55
60	0.31	0.65	0.30	0.89
85	0.14	0.03	0.00	0.27
85	0.23	0.10	0.01	0.47
85	0.31	0.27	0.04	0.78

4. Discussion

The study results support the importance of oxidative stress pathways in the pathogenesis of MDD. Among oxidative stress parameters tested, urine 3-NT seems to have the greatest potential in distinguishing between depressed and healthy people. Urine 3-NT is a product of tyrosine nitration, mediated by RNS—nitrogen dioxide and peroxynitrite anion—and is considered a marker of NO-dependent nitrosative stress. It was previously found to be upregulated in depressed patients [56], in middle-aged women who were more prone to depression [57], adolescents with the depressive disorder [58], and post-stroke patients with depression [59]. All of the abovementioned studies concentrated on 3-NT blood levels. Interestingly, previous studies suggest that nitrotyrosine levels may be reduced by the glutathione precursor, N-acetyl cysteine [60], which is known for its antidepressant properties [61]. Nitrotyrosine has also been associated with neurodegeneration, especially in the dopamine neurons [62], which could be linked to the fact that tyrosine is the biological precursor to dopamine. Urine 3-NT was previously described as a marker of neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases [63]. This could support the concept of the common underpinning of depression and neurodegenerative disorders, as postulated by Maes et al. [10]. Urine 3-NT has also been found to be upregulated in bipolar disorder [64].

Lipid disturbances are frequently observed in patients with mental disorders. This is not surprising, taking into account that lipids constitute as much as 50% of dry brain mass, and the proportion of lipids in brain tissue is the second largest after adipose tissue [65]. Alterations in lipids levels were previously described in different mental disorders, including depression [66]. Lower serum HDL concentrations were found in depressed patients and in depressed men who had attempted suicide [67]. However, in a meta-analysis by Li et al. [68], suicidal attempts in MDD have been linked to lower LDL and total cholesterol levels, but not to alterations in HDL or TG. Lower HDL levels may be characteristic of a subgroup of depressive patients above 40 years old, as described in the meta-analysis of Bharti et al. [69]. Decreased HDL was found in patients with a first episode of MDD [70], MDD and anhedonia [71], and post-stroke depression [72]. A higher LDL/HDL ratio was found in depressive patients [73]. Lower HDL was also associated with an immune-metabolic subtype of depression [74]. In contrast, in the meta-analysis of Shin et al. [75], higher HDL levels were linked to a higher incidence of depression, particularly in women.

The lack of race and geographic diversity in this study it is worth noting, since all study participants were Polish and of Caucasian race. On the other hand, it should be noted that MDD patients received different antidepressant drugs before their inclusion in the study. Hence, it is unclear whether the differences observed between MDD patients and healthy controls are only due to the presence or absence of depressive illness, or if they might be related to the previously received antidepressant treatment.

5. Conclusions

The biomarkers research in the field of psychiatry constantly develops, offering a plethora of potential new MDD biomarkers. O&NS and lipid disturbances play an important role in MDD etiopathogenesis [76] and thus constitute a promising source of biomarkers. However, the specificity and sensitivity of any biomarker regarded alone remain almost certainly insufficient. Combined determination of urine O&NS marker 3-NT and blood HDL gives promise as a potential marker of MDD. Nevertheless, the clinical usefulness of such a biomarker combination should be further assessed in a dedicated study. There is a need to construct a validated, multi-dimensional biomarker panel to support the diagnostic process, optimal treatment matching, or outcomes prognosis.

6. Limitations

Among the study limitations, the small sample size, the need of controlling for age in the results, and the diversity of antidepressant treatments received by the individuals from the study group should be noted. Moreover, a potentially confounding factor is the

higher proportion of smokers in the study group. It is also necessary to admit that some determinants are missing—a few study participants were not screened for all the biological parameters described.

References

1. Smith, K. Mental Health: A World of Depression. *Nature* **2014**, *515*, 180–181. [CrossRef] [PubMed]
2. Terrill, A. Global Disability Adjusted Life-Years Attributed to Mental Disorders Increased From 1990 to 2019. Available online: https://www.psychiatryadvisor.com/home/topics/general-psychiatry/2019-global-burden-of-diseases-found-dalys-increased-from-3-1-to-4-9-percent/ (accessed on 10 October 2022).
3. Czarny, P.; Wigner, P.; Galecki, P.; Sliwinski, T. The Interplay between Inflammation, Oxidative Stress, DNA Damage, DNA Repair and Mitochondrial Dysfunction in Depression. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2018**, *80*, 309–321. [CrossRef] [PubMed]
4. Liu, T.; Zhong, S.; Liao, X.; Chen, J.; He, T.; Lai, S.; Jia, Y. A Meta-Analysis of Oxidative Stress Markers in Depression. *PLoS ONE* **2015**, *10*, e0138904. [CrossRef] [PubMed]
5. Gawryluk, J.W.; Wang, J.-F.; Andreazza, A.C.; Shao, L.; Young, L.T. Decreased Levels of Glutathione, the Major Brain Antioxidant, in Post-Mortem Prefrontal Cortex from Patients with Psychiatric Disorders. *Int. J. Neuropsychopharmacol.* **2011**, *14*, 123–130. [CrossRef] [PubMed]
6. Itoh, K.; Chiba, T.; Takahashi, S.; Ishii, T.; Igarashi, K.; Katoh, Y.; Oyake, T.; Hayashi, N.; Satoh, K.; Hatayama, I.; et al. An Nrf2/Small Maf Heterodimer Mediates the Induction of Phase II Detoxifying Enzyme Genes through Antioxidant Response Elements. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 313–322. [CrossRef]
7. Maes, M.; Carvalho, A.F. The Compensatory Immune-Regulatory Reflex System (CIRS) in Depression and Bipolar Disorder. *Mol. Neurobiol.* **2018**, *55*, 8885–8903. [CrossRef]
8. Maes, M.; Mihaylova, I.; Kubera, M.; Uytterhoeven, M.; Vrydags, N.; Bosmans, E. Increased Plasma Peroxides and Serum Oxidized Low Density Lipoprotein Antibodies in Major Depression: Markers That Further Explain the Higher Incidence of Neurodegeneration and Coronary Artery Disease. *J. Affect. Disord.* **2010**, *125*, 287–294. [CrossRef]
9. Hussain, M.; Kumar, P.; Khan, S.; Gordon, D.; Khan, S. Similarities Between Depression and Neurodegenerative Diseases: Pathophysiology, Challenges in Diagnosis and Treatment Options. *Cureus* **2020**, *12*, e11613. [CrossRef]
10. Maes, M.; Yirmyia, R.; Noraberg, J.; Brene, S.; Hibbeln, J.; Perini, G.; Kubera, M.; Bob, P.; Lerer, B.; Maj, M. The Inflammatory & Neurodegenerative (I&ND) Hypothesis of Depression: Leads for Future Research and New Drug Developments in Depression. *Metab. Brain Dis.* **2009**, *24*, 27–53. [CrossRef]
11. Arnone, D.; Saraykar, S.; Salem, H.; Teixeira, A.L.; Dantzer, R.; Selvaraj, S. Role of Kynurenine Pathway and Its Metabolites in Mood Disorders: A Systematic Review and Meta-Analysis of Clinical Studies. *Neurosci. Biobehav. Rev.* **2018**, *92*, 477–485. [CrossRef]
12. Cheignon, C.; Tomas, M.; Bonnefont-Rousselot, D.; Faller, P.; Hureau, C.; Collin, F. Oxidative Stress and the Amyloid Beta Peptide in Alzheimer's Disease. *Redox. Biol.* **2018**, *14*, 450–464. [CrossRef]
13. Butterfield, D.A.; Boyd-Kimball, D. Oxidative Stress, Amyloid-β Peptide, and Altered Key Molecular Pathways in the Pathogenesis and Progression of Alzheimer's Disease. *J. Alzheimers. Dis.* **2018**, *62*, 1345–1367. [CrossRef]

14. Mahgoub, N.; Alexopoulos, G.S. Amyloid Hypothesis: Is There a Role for Antiamyloid Treatment in Late-Life Depression? *Am J. Geriatr. Psychiatry* **2016**, *24*, 239–247. [CrossRef]
15. van Dyck, C.H.; O'Dell, R.S.; Mecca, A.P. Amyloid-Associated Depression-or Not? *Biol. Psychiatry* **2021**, *89*, 737–738. [CrossRef]
16. Harrington, K.D.; Lim, Y.Y.; Gould, E.; Maruff, P. Amyloid-Beta and Depression in Healthy Older Adults: A Systematic Review. *Aust. N. Z. J. Psychiatry* **2015**, *49*, 36–46. [CrossRef]
17. Wu, K.-Y.; Hsiao, I.-T.; Chen, C.-S.; Chen, C.-H.; Hsieh, C.-J.; Wai, Y.-Y.; Chang, C.-J.; Tseng, H.-J.; Yen, T.-C.; Liu, C.-Y.; et al. Increased Brain Amyloid Deposition in Patients with a Lifetime History of Major Depression: Evidenced on 18F-Florbetapir (AV-45/Amyvid) Positron Emission Tomography. *Eur. J. Nucl. Med. Mol. Imaging* **2014**, *41*, 714–722. [CrossRef]
18. Kumar, A.; Kepe, V.; Barrio, J.R.; Siddarth, P.; Manoukian, V.; Elderkin-Thompson, V.; Small, G.W. Protein Binding in Patients with Late-Life Depression. *Arch. Gen. Psychiatry* **2011**, *68*, 1143–1150. [CrossRef]
19. Krell-Roesch, J.; Lowe, V.J.; Neureiter, J.; Pink, A.; Roberts, R.O.; Mielke, M.M.; Vemuri, P.; Stokin, G.B.; Christianson, T.J.; Jack, C.R.; et al. Depressive and Anxiety Symptoms and Cortical Amyloid Deposition among Cognitively Normal Elderly Persons: The Mayo Clinic Study of Aging. *Int. Psychogeriatr.* **2018**, *30*, 245–251. [CrossRef]
20. Wu, K.-Y.; Lin, K.-J.; Chen, C.-H.; Liu, C.-Y.; Wu, Y.-M.; Chen, C.-S.; Yen, T.-C.; Hsiao, I.-T. Decreased Cerebral Amyloid-β Depositions in Patients With a Lifetime History of Major Depression With Suspected Non-Alzheimer Pathophysiology. *Front. Aging Neurosci.* **2022**, *14*, 857940. [CrossRef]
21. Mackin, R.S.; Insel, P.S.; Landau, S.; Bickford, D.; Morin, R.; Rhodes, E.; Tosun, D.; Rosen, H.J.; Butters, M.; Aisen, P.; et al. Late-Life Depression Is Associated with Reduced Cortical Amyloid Burden: Findings From the Alzheimer's Disease Neuroimaging Initiative Depression Project. *Biol. Psychiatry* **2021**, *89*, 757–765. [CrossRef]
22. Nobis, A.; Zalewski, D.; Waszkiewicz, N. Peripheral Markers of Depression. *J. Clin. Med.* **2020**, *9*, 3793. [CrossRef] [PubMed]
23. Chen, J.; Bai, S.-J.; Li, W.; Zhou, C.; Zheng, P.; Fang, L.; Wang, H.; Liu, Y.; Xie, P. Urinary Biomarker Panel for Diagnosing Patients with Depression and Anxiety Disorders. *Transl. Psychiatry* **2018**, *8*, 192. [CrossRef] [PubMed]
24. Lopresti, A.L.; Maker, G.L.; Hood, S.D.; Drummond, P.D. A Review of Peripheral Biomarkers in Major Depression: The Potential of Inflammatory and Oxidative Stress Biomarkers. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2014**, *48*, 102–111. [CrossRef] [PubMed]
25. Carvalho, A.F.; Solmi, M.; Sanches, M.; Machado, M.O.; Stubbs, B.; Ajnakina, O.; Sherman, C.; Sun, Y.R.; Liu, C.S.; Brunoni, A.R.; et al. Evidence-Based Umbrella Review of 162 Peripheral Biomarkers for Major Mental Disorders. *Transl. Psychiatry* **2020**, *10*, 152. [CrossRef] [PubMed]
26. van Buel, E.M.; Meddens, M.J.M.; Arnoldussen, E.A.; van den Heuvel, E.R.; Bohlmeijer, W.C.; den Boer, J.A.; Muller Kobold, A.; Boonman-de Winter, L.J.M.; van Rumpt, D.; Timmers, L.F.J.; et al. Major Depressive Disorder Is Associated with Changes in a Cluster of Serum and Urine Biomarkers. *J. Psychosom. Res.* **2019**, *125*, 109796. [CrossRef]
27. Sheehan, D.V.; Lecrubier, Y.; Sheehan, K.H.; Amorim, P.; Janavs, J.; Weiller, E.; Hergueta, T.; Baker, R.; Dunbar, G.C. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* **1998**, *59* (Suppl. 20), 22–33.
28. Beck, A.T.; Ward, C.H.; Mendelson, M.; Mock, J.; Erbaugh, J. An Inventory for Measuring Depression. *Arch. Gen. Psychiatry* **1961**, *4*, 561–571. [CrossRef]
29. Hamilton, M. A Rating Scale for Depression. *J. Neurol. Neurosurg. Psychiatry* **1960**, *23*, 56–62. [CrossRef]
30. Thompson, E. Hamilton Rating Scale for Anxiety (HAM-A). *Occup. Med.* **2015**, *65*, 601. [CrossRef]
31. Aebi, H. Catalase in Vitro. In *Methods in Enzymology*; Oxygen Radicals in Biological Systems; Academic Press: Cambridge, MA, USA, 1984; Volume 105, pp. 121–126.
32. Misra, H.P.; Fridovich, I. The Role of Superoxide Anion in the Autoxidation of Epinephrine and a Simple Assay for Superoxide Dismutase. *J. Biol. Chem.* **1972**, *247*, 3170–3175. [CrossRef]
33. Paglia, D.E.; Valentine, W.N. Studies on the Quantitative and Qualitative Characterization of Erythrocyte Glutathione Peroxidase. *J. Lab. Clin. Med.* **1967**, *70*, 158–169.
34. Moron, M.S.; Depierre, J.W.; Mannervik, B. Levels of Glutathione, Glutathione Reductase and Glutathione S-Transferase Activities in Rat Lung and Liver. *Biochim. Et Biophys. Acta (BBA)—Gen. Subj.* **1979**, *582*, 67–78. [CrossRef]
35. Erel, O. A New Automated Colorimetric Method for Measuring Total Oxidant Status. *Clin. Biochem.* **2005**, *38*, 1103–1111. [CrossRef]
36. Kalousová, M.; Skrha, J.; Zima, T. Advanced Glycation End-Products and Advanced Oxidation Protein Products in Patients with Diabetes Mellitus. *Physiol. Res.* **2002**, *51*, 597–604.
37. Borys, J.; Maciejczyk, M.; Krętowski, A.J.; Antonowicz, B.; Ratajczak-Wrona, W.; Jabłońska, E.; Załęski, P.; Waszkiel, D.; Ładny, J.R.; Żukowski, P.; et al. The Redox Balance in Erythrocytes, Plasma, and Periosteum of Patients with Titanium Fixation of the Jaw. *Front. Physiol.* **2017**, *8*, 386. [CrossRef]
38. Gęgotek, A.; Rybałtowska-Kawałko, P.; Skrzydlewska, E. Rutin as a Mediator of Lipid Metabolism and Cellular Signaling Pathways Interactions in Fibroblasts Altered by UVA and UVB Radiation. *Oxidative Med. Cell. Longev.* **2017**, *2017*, e4721352. [CrossRef]
39. Walker, J.M. The Bicinchoninic Acid (BCA) Assay for Protein Quantitation. *Methods Mol. Biol.* **1994**, *32*, 5–8. [CrossRef]
40. Pawlukianiec, C.; Gryciuk, M.E.; Mil, K.M.; Żendzian-Piotrowska, M.; Zalewska, A.; Maciejczyk, M. A New Insight into Meloxicam: Assessment of Antioxidant and Anti-Glycating Activity in In Vitro Studies. *Pharmaceuticals* **2020**, *13*, 240. [CrossRef]

41. Funder, D.C.; Ozer, D.J. Evaluating Effect Size in Psychological Research: Sense and Nonsense. *Adv. Methods Pract. Psychol. Sci.* **2019**, *2*, 156–168. [CrossRef]
42. Statistical Power Analysis for the Behavioral Sciences | Jacob Cohen. Available online: https://www.taylorfrancis.com/books/mono/10.4324/9780203771587/statistical-power-analysis-behavioral-sciences-jacob-cohen (accessed on 2 November 2022).
43. Benjamini, Y.; Hochberg, Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J. R. Stat. Soc. Ser. B* **1995**, *57*, 289–300. [CrossRef]
44. Khamis, H. Measures of Association: How to Choose? *J. Diagn. Med. Sonogr.* **2008**, *24*, 155–162. [CrossRef]
45. Danieluk, B. *Application of Logistic Regression in Experimental Research—Back Content of Social Psychological Bulletin (Psychologia Społeczna). (2–3(14)/2010)*; Wydawnictwo Naukowe Scholar: Warsaw, Poland, 2010; ISSN 896-1800.
46. R: The R Project for Statistical Computing. Available online: https://www.r-project.org/ (accessed on 23 November 2022).
47. Ben-Shachar, M.S.; Lüdecke, D.; Makowski, D. Effectsize: Estimation of Effect Size Indices and Standardized Parameters. *J. Open Source Softw.* **2020**, *5*, 2815. [CrossRef]
48. Applied Regression 3E. Available online: https://socialsciences.mcmaster.ca/jfox/Books/Companion/ (accessed on 2 November 2022).
49. Harrell, F., Jr. Hmisc: Harrell Miscellaneous. R package version 4.7-0. 2022. Available online: https://CRAN.R-project.org/package=Hmisc (accessed on 24 October 2022).
50. Lüdecke, D. Ggeffects: Tidy Data Frames of Marginal Effects from Regression Models. *J. Open Source Softw.* **2018**, *3*, 772. [CrossRef]
51. Lüdecke, D. sjPlot: Data Visualization for Statistics in Social Science. R Package Version 2.8.10. 2021. Available online: https://CRAN.R-project.org/package=sjPlot (accessed on 29 October 2022).
52. Makowski, D.; Ben-Shachar, M.; Patil, I.; Lüdecke, D. Automated Results Reporting as a Practical Tool to Improve Reproducibility and Methodological Best Practices Adoption. 2021. Available online: https://github.com/easystats/report (accessed on 22 October 2022).
53. Mangiafico, S. rcompanion: Functions to Support Extension Education Program Evaluation. R package version 2.4.15. 2022. Available online: https://CRAN.R-project.org/package=rcompanion (accessed on 22 October 2022).
54. Revelle, W. psych: Procedures for Psychological, Psychometric, and Personality Research. Northwestern University, Evanston, Illinois. R Package Version 2.1.6. 2021. Available online: https://CRAN.R-project.org/package=psych (accessed on 22 October 2022).
55. Create Elegant Data Visualisations Using the Grammar of Graphics. Available online: https://ggplot2.tidyverse.org/ (accessed on 23 November 2022).
56. Baek, D.; Park, Y. Association between Erythrocyte N-3 Polyunsaturated Fatty Acids and Biomarkers of Inflammation and Oxidative Stress in Patients with and without Depression. *Prostaglandins Leukot. Essent. Fat. Acids* **2013**, *89*, 291–296. [CrossRef] [PubMed]
57. Pasquali, M.A.; Harlow, B.L.; Soares, C.N.; Otto, M.W.; Cohen, L.S.; Minuzzi, L.; Gelain, D.P.; Moreira, J.C.F.; Frey, B.N. A Longitudinal Study of Neurotrophic, Oxidative, and Inflammatory Markers in First-Onset Depression in Midlife Women. *Eur. Arch. Psychiatry Clin. Neurosci.* **2018**, *268*, 771–781. [CrossRef]
58. Katrenčíková, B.; Vaváková, M.; Paduchová, Z.; Nagyová, Z.; Garaiova, I.; Muchová, J.; Ďuračková, Z.; Trebatická, J. Oxidative Stress Markers and Antioxidant Enzymes in Children and Adolescents with Depressive Disorder and Impact of Omega-3 Fatty Acids in Randomised Clinical Trial. *Antioxidants* **2021**, *10*, 1256. [CrossRef]
59. Cichoń, N.; Bijak, M.; Miller, E.; Niwald, M.; Saluk, J. Poststroke Depression as a Factor Adversely Affecting the Level of Oxidative Damage to Plasma Proteins during a Brain Stroke. *Oxidative Med. Cell. Longev.* **2015**, *2015*, e408745. [CrossRef]
60. Ivanovski, O.; Szumilak, D.; Nguyen-Khoa, T.; Ruellan, N.; Phan, O.; Lacour, B.; Descamps-Latscha, B.; Dreeke, T.B.; Massy, Z.A. The Antioxidant N-Acetylcysteine Prevents Accelerated Atherosclerosis in Uremic Apolipoprotein E Knockout Mice. *Kidney Int.* **2005**, *67*, 2288–2294. [CrossRef]
61. Yang, C.; Bosker, F.J.; Li, J.; Schoevers, R.A. N-Acetylcysteine as Add-on to Antidepressant Medication in Therapy Refractory Major Depressive Disorder Patients with Increased Inflammatory Activity: Study Protocol of a Double-Blind Randomized Placebo-Controlled Trial. *BMC Psychiatry* **2018**, *18*, 279. [CrossRef]
62. Kuhn, D.M.; Sakowski, S.A.; Sadidi, M.; Geddes, T.J. Nitrotyrosine as a Marker for Peroxynitrite-Induced Neurotoxicity: The Beginning or the End of the End of Dopamine Neurons? *J. Neurochem.* **2004**, *89*, 529–536. [CrossRef]
63. Bandookwala, M.; Sengupta, P. 3-Nitrotyrosine: A Versatile Oxidative Stress Biomarker for Major Neurodegenerative Diseases. *Int. J. Neurosci.* **2020**, *130*, 1047–1062. [CrossRef] [PubMed]
64. Andreazza, A.C.; Kapczinski, F.; Kauer-Sant'Anna, M.; Walz, J.C.; Bond, D.J.; Gonçalves, C.A.; Young, L.T.; Yatham, L.N. 3-Nitrotyrosine and Glutathione Antioxidant System in Patients in the Early and Late Stages of Bipolar Disorder. *J. Psychiatry Neurosci.* **2009**, *34*, 263–271.
65. Hamilton, J.A.; Hillard, C.J.; Spector, A.A.; Watkins, P.A. Brain Uptake and Utilization of Fatty Acids, Lipids and Lipoproteins: Application to Neurological Disorders. *J. Mol. Neurosci.* **2007**, *33*, 2–11. [CrossRef] [PubMed]
66. Kułak-Bejda, A.; Bejda, G.; Lech, M.; Waszkiewicz, N. Are Lipids Possible Markers of Suicide Behaviors? *J. Clin. Med.* **2021**, *10*, 333. [CrossRef] [PubMed]

67. Maes, M.; Smith, R.; Christophe, A.; Vandoolaeghe, E.; Van Gastel, A.; Neels, H.; Demedts, P.; Wauters, A.; Meltzer, H.Y. Lower Serum High-Density Lipoprotein Cholesterol (HDL-C) in Major Depression and in Depressed Men with Serious Suicidal Attempts: Relationship with Immune-Inflammatory Markers. *Acta Psychiatr. Scand.* **1997**, *95*, 212–221. [CrossRef] [PubMed]

68. Li, H.; Zhang, X.; Sun, Q.; Zou, R.; Li, Z.; Liu, S. Association between Serum Lipid Concentrations and Attempted Suicide in Patients with Major Depressive Disorder: A Meta-Analysis. *PLoS ONE* **2020**, *15*, e0243847. [CrossRef]

69. Bharti, V.; Bhardwaj, A.; Hood, K.; Elias, D.A.; Metcalfe, A.W.S.; Kim, J.S. A Systematic Review and Meta-Analysis of Lipid Metabolomic Signatures of Major Depressive Disorder. *J. Psychiatr. Res.* **2021**, *139*, 197–205. [CrossRef]

70. Wei, Y.-G.; Cai, D.-B.; Liu, J.; Liu, R.-X.; Wang, S.-B.; Tang, Y.-Q.; Zheng, W.; Wang, F. Cholesterol and Triglyceride Levels in First-Episode Patients with Major Depressive Disorder: A Meta-Analysis of Case-Control Studies. *J. Affect Disord.* **2020**, *266*, 465–472. [CrossRef]

71. Moreira, F.P.; Jansen, K.; Cardoso, T.d.A.; Mondin, T.C.; Vieira, I.S.; Magalhães, P.V.d.S.; Kapczinski, F.; Souza, L.D.d.M.; da Silva, R.A.; Oses, J.P.; et al. Metabolic Syndrome, Depression and Anhedonia among Young Adults. *Psychiatry Res.* **2019**, *271*, 306–310. [CrossRef]

72. Shen, H.; Tu, X.; Luan, X.; Zeng, Y.; He, J.; Tang, W. Serum Lipid Profiles and Post-Stroke Depression in Acute Ischemic Stroke Patients. *Neuropsychiatr. Dis. Treat.* **2019**, *15*, 1573–1583. [CrossRef]

73. Wagner, C.J.; Musenbichler, C.; Böhm, L.; Färber, K.; Fischer, A.-I.; von Nippold, F.; Winkelmann, M.; Richter-Schmidinger, T.; Mühle, C.; Kornhuber, J.; et al. LDL Cholesterol Relates to Depression, Its Severity, and the Prospective Course. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2019**, *92*, 405–411. [CrossRef]

74. Alshehri, T.; Mook-Kanamori, D.O.; Willems van Dijk, K.; Dinga, R.; Penninx, B.W.J.H.; Rosendaal, F.R.; le Cessie, S.; Milaneschi, Y. Metabolomics Dissection of Depression Heterogeneity and Related Cardiometabolic Risk. *Psychol. Med.* **2021**, 1–10. [CrossRef]

75. Shin, J.Y.; Suls, J.; Martin, R. Are Cholesterol and Depression Inversely Related? A Meta-Analysis of the Association between Two Cardiac Risk Factors. *Ann. Behav. Med.* **2008**, *36*, 33–43. [CrossRef]

76. Black, C.N.; Bot, M.; Scheffer, P.G.; Cuijpers, P.; Penninx, B.W. Is Depression Associated with Increased Oxidative Stress? A Systematic Review and Meta-Analysis. *Psychoneuroendocrinology* **2015**, *51*, 164–175. [CrossRef]

9. Streszczenie w języku polskim

9.1 Wstęp

Depresja (zaburzenie depresyjne, ang. *Major Depressive Disorder*, MDD) jest jednym z najczęściej występujących zaburzeń psychicznych na świecie. Etiopatogeneza depresji jest wieloczynnikowa i w dalszym ciągu pozostaje nie w pełni wyjaśniona. Pośród czynników biologicznych mających wpływ na ujawnienie się depresji, należy wymienić predyspozycje genetyczne, zaburzenia przekaźnictwa monoaminergicznego, rozregulowanie osi stresu (podwzgórze – przysadka – nadnercza) oraz stan nierównowagi pomiędzy procesami zapalnymi i przeciwzapalnymi. Stres oksydacyjny i nitrozowy (O&NS) jest również wymieniany jako jeden z kluczowych czynników biologicznych zaangażowanych w powstawanie depresji. Jest to miara wpływu wywieranego na organizm przez reaktywne formy tlenu (ROS) i azotu (RNS). W warunkach fizjologii ROS i RNS są neutralizowane przez organizm na kilka sposobów. Jednym z nich jest tzw. wymiatanie wolnych rodników, np. poprzez zredukowany glutation. Innym – dezaktywacja enzymatyczna, np. poprzez dysmutazę ponadtlenkową (SOD), peroksydazę glutationową (GPx) i katalazę (CAT). W sytuacji niedostatecznego równoważenia procesów oksydacyjnych przez układy antyoksydacyjne, ROS i RNS uszkadzają makrocząsteczki komórkowe, takie jak białka, lipidy i kwas deoksyrybonukleinowy (DNA), nasilając proces zapalny i powodując dalsze uszkodzenia.

Istnieje ścisłe powiązanie O&NS i procesów neurodegeneracyjnych, charakterystycznych dla chorób neurozwyrodnieniowych, takich jak choroba Alzheimera. Badania sugerują że depresja może być postrzegana jako choroba neurodegeneracyjna. W populacji chorych na depresję, szczególnie w starszym wieku, odnotowano zmienione poziomy złogów β-amyloidu w korze mózgowej.

Współczesne badania naukowe w dziedzinie psychiatrii koncentrują się m.in. na poszukiwaniu biomarkerów zaburzeń psychicznych. Rosnąca liczba dowodów naukowych wskazuje na istnienie szeregu biochemicznych markerów MDD, na podstawie których można odróżnić pacjentów chorujących na depresję od zdrowej populacji. Markery nasilenia stresu oksydacyjnego i nitrozowego mogą być interesujące w kontekście diagnozowania i leczenia depresji oraz głębszego rozumienia mechanizmów patogenetycznych odpowiedzialnych za ujawnienie się zaburzenia. Biomarkery oznaczane w moczu stanowią interesującą alternatywę dla biomarkerów z krwi, ze względu na prosty i nieinwazyjny sposób pobierania materiału biologicznego oraz fakt, że stężenie biomarkerów w moczu może przynajmniej częściowo odzwierciedlać ich stężenie we krwi.

9.2 Cel pracy

Celem pracy było poszukiwanie potencjalnych obwodowych biomarkerów depresji.

9.3 Materiał i metody

Do badania zrekrutowano 29 pacjentów z rozpoznaniem MDD oraz 30 zdrowych osób jako grupę kontrolną. Rozpoznanie depresji (tj. epizodu depresyjnego lub zaburzenia depresyjnego nawracającego) było stawiane w oparciu o kryteria Międzynarodowej Klasyfikacji Chorób, wydania 11 (ICD-11) i potwierdzone przez doświadczonego psychiatrę. W celu wykluczenia innych potencjalnych jednostek psychiatrycznych, stosowano ustrukturyzowany kwestionariusz wywiadu (MINI). Uczestników badania oceniono przy pomocy skal psychometrycznych – skali depresji Becka 1 (BDI), skali depresji Hamiltona (HAM-D) oraz skali lęku Hamiltona (HAM-A). Czas trwania choroby mierzono jako liczbę lat od początku pierwszego epizodu depresyjnego.

U każdego uczestnika badania wykonano podstawowe oznaczenia z krwi – morfologia, stężenia potasu, sodu, kreatyniny, aminotransferaza alaninowa (ALT), aminotransferaza asparaginianowa (AST), białko C-reaktywne (CRP), hormon stymulujący tarczycę (TSH), cholesterol całkowity (TC), lipoproteiny o niskiej gęstości (LDL), lipoproteiny o wysokiej gęstości (HDL), trójglicerydy (TGA).

Pobrano próbki moczu, w których oceniono następujące parametry: całkowita pojemność antyoksydacyjna (TAC), katalaza (CAT), peroksydaza glutationowa (GPx), dysmutaza ponadtlenkowa (SOD), zredukowany glutation (GSH), całkowity status oksydacyjny (TOS), 3-nitrotyrozyna (3-NT), końcowe produkty zaawansowanej glikacji (AGE), produkty zaawansowanego utleniania białek (AOPP), N-formylokinurenina (NFKN), kinurenina (KN), tryptofan (TRY) i β-amyloid.

9.4 Wyniki

Grupa chorych na depresję charakteryzowała się wyższymi średnimi stężeniami TGA w surowicy oraz SOD, 3-NT, CAT, GSH i TRY w moczu, oraz niższymi stężeniami HDL w surowicy.

Wyniki skal psychometrycznych HAM-A, HAM-D i BDI oraz czynnik czasu trwania choroby wykazały istotne powiązania ze stężeniami HDL i TGA w surowicy krwi oraz stężeniami SOD, 3-NT, CAT i TRY w moczu. Stężenie GSH w moczu korelowało z wynikiem HAM-A.

Zaobserwowano ujemną korelację z HDL — wyższy wynik skal, podobnie jak dłuższy czas trwania choroby, korelował ze spadkiem stężeń HDL. Wzrost

wyników skal psychometrycznych i dłuższy czas trwania choroby korelował ze wzrostem poziomu TGA, SOD, 3-NT, CAT, TRY i GSH.

Wzrost stężenia HDL o 1,00 mg/dl obniżał logarytm ilorazu szans wystąpienia depresji o 0,07 – przy założeniu, że kontrolowano inne predyktory. Zwiększenie stężenia 3-NT o 1,00 nmol/mg białka zwiększyło logarytm ilorazu szans wystąpienia depresji o 15,52. Z analizowanych danych wynika że pacjenci u których stwierdzono stężenie HDL < 40 mg/dl i stężenie 3-NT > 0,3 nmol/mg białka byli bardziej narażeni na wystąpienie depresji, podczas gdy pacjenci u których stwierdzono stężenie HDL > 80 mg/dl i stężenie 3-NT < 0,15 nmol/mg białka byli mniej podatni na wystąpienie depresji.

9.5 Wnioski

1. Populacja osób chorujących na depresję charakteryzuje się większym nasileniem stresu oksydacyjnego i nitrozowego w porównaniu do populacji zdrowej.
2. Marker stresu nitrozowego – 3-nitrotyrozyna (3-NT) – oznaczany w moczu, w połączeniu z lipoproteiną wysokiej gęstości (HDL) oznaczaną w surowicy może stanowić potencjalny marker depresji.

10. Streszczenie w języku angielskim

10.1 Introduction

Major Depressive Disorder (MDD) is one of the most common mental disorders in the world. The etiopathogenesis of depression is complex and still not fully understood. Among the biological factors involved in depression, genetic predisposition, disturbances of monoaminergic transmission, dysregulation of the stress axis (hypothalamic – pituitary – adrenal glands) and the state of imbalance between inflammatory and anti-inflammatory processes should be mentioned. Oxidative and nitrosative stress (O&NS) is also considered as one of the key biological factors involved in depression pathogenesis. Oxidative and nitrosative stress is a measure of the effect of reactive oxygen (ROS) and nitrogen (RNS) species on the body. Under physiological conditions, ROS and RNS are neutralized by the body in several ways. One of them is the so-called free radicals scavenging, e.g. through reduced glutathione. Another is enzymatic inactivation, e.g. by superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT). When oxidative processes are not sufficiently balanced by antioxidant systems, ROS and RNS damage cellular macromolecules such as proteins, lipids and deoxyribonucleic acid (DNA), increasing inflammation and causing further damage.

There is a close connection between O&NS and the neurodegenerative processes that are characteristic of neurodegenerative diseases such as Alzheimer's disease. Research suggests that depression can be considered as a neurodegenerative disease. In the population of depressive patients, especially in the elderly, altered levels of β-amyloid deposits in the cerebral cortex have been noted.

Contemporary research in the field of psychiatry focuses, among others, on on the search for biomarkers of mental disorders. A growing body of scientific evidence points to the existence of a number of biochemical markers of MDD that can be used to distinguish depressed patients from the healthy population. Markers of the severity of oxidative and nitrosative stress may be of interest in the context of diagnosing and treating depression as well as a deeper understanding of the pathogenetic mechanisms responsible for the manifestation of the disorder. Urine biomarkers are an interesting alternative to blood biomarkers due to the simple and non-invasive way of sample collection and the fact that the concentration of biomarkers in the urine may at least partially reflect their concentration in the blood.

10.2 Aim of the study

The aim of the study was to search for potential peripheral biomarkers of depression.

10.3 Material and Methods

29 patients diagnosed with MDD and 30 healthy volunteers were recruited for the study. The diagnosis of depression (i.e. a depressive episode or recurrent depressive disorder) was based on the International Classification of Diseases, 11th edition (ICD-11) criteria and confirmed by an experienced psychiatrist. A Structured Interview Questionnaire (MINI) was used to exclude other potential psychiatric entities. Study participants were assessed using psychometric scales – the Beck depression inventory 1 (BDI), the Hamilton depression scale (HAM-D) and the Hamilton anxiety scale (HAM-A). The duration of illness was measured as the number of years from the onset of the first depressive episode.

Basic blood tests – blood count, potassium, sodium, creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), thyroid-stimulating hormone (TSH), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) concentration – were performed in each study participant.

Urine samples were collected and the following parameters were assessed: total antioxidant capacity (TAC), CAT, GPx, SOD, reduced glutathione (GSH), total oxidative status (TOS), 3-nitrotyrosine (3-NT), advanced glycation end-products (AGE), advanced protein oxidation products (AOPP), N-formylkynurenine (NFKN), kynurenine (KN), tryptophan (TRY) and β-amyloid.

10.4 Results

The group of patients with depression was characterized by higher mean concentrations of TGA in the serum, higher SOD, 3-NT, CAT, GSH and TRY in the urine, and lower concentrations of HDL in the serum.

The results of the HAM-A, HAM-D and BDI psychometric scales as well as the disease duration factor showed significant associations with serum HDL and TGA concentrations as well as SOD, 3-NT, CAT and TRY concentrations in urine. GSH concentration in the urine correlated with the HAM-A score.

A negative correlation with HDL was observed – a higher scale score, as well as a longer duration of the disease, correlated with a decrease in HDL concentrations. The increase in the scores of psychometric scales and the longer duration of the

disease correlated with the increase in the level of TGA, SOD, 3-NT, CAT, TRY and GSH.

An increase in HDL of 1.00 mg/dl reduced the log odds ratio for depression by 0.07, assuming other predictors were controlled for. Increasing the 3-NT concentration by 1.00 nmol/mg protein increased the log odds ratio of depression by 15.52. The analyzed data show that patients with HDL concentration < 40 mg/dl and 3-NT concentration > 0.3 nmol/mg protein were more prone to depression, while patients with HDL concentration > 80 mg/dl and 3-NT concentration < 0.15 nmol/mg protein were less likely to develop depression.

10.5 Conclusions

1. The population of depressive patients is characterized by a higher intensity of oxidative and nitrosative stress compared to the healthy population.

2. Nitrosative stress marker – 3-nitrotyrosine (3-NT) – determined in the urine, in combination with high-density lipoprotein (HDL) determined in the blood, may be a potential biomarker of depression.

11. Piśmiennictwo

1. Smith, K. Mental health: a world of depression. *Nature* **2014**, 515, 180-181

2. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* **2022**, *9*, 137–150.

3. ICD-11 for Mortality and Morbidity Statistics. Dostępne online 30.06.2023 https://icd.who.int/browse11/l-m/en.

4. Czarny, P.; Wigner, P.; Galecki, P.; Sliwinski, T. The Interplay between Inflammation, Oxidative Stress, DNA Damage, DNA Repair and Mitochondrial Dysfunction in Depression. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2018**, *80*, 309–321.

5. Liu, T.; Zhong, S.; Liao, X.; Chen, J.; He, T.; Lai, S.; Jia, Y. A Meta-Analysis of Oxidative Stress Markers in Depression. *PLoS ONE* **2015**, *10*, e0138904.

6. Gawryluk, J. W., Wang, J.-F., Andreazza, A. C., Shao, L. & Young, L. T. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *Int. J. Neuropsychopharmacol.* **2011**, *14*, 123–130.

7. Maes, M.; Carvalho, A. F. The Compensatory Immune-Regulatory Reflex System (CIRS) in Depression and Bipolar Disorder. *Mol. Neurobiol.* **2018**, *55*, 8885–8903.

8. Maes, M.; Mihaylova, I.; Kubera, M.; Uytterhoeven, M.; Vrydags, N.; Bosmans, E. Increased Plasma Peroxides and Serum Oxidized Low Density Lipoprotein Antibodies in Major Depression: Markers That Further Explain the Higher Incidence of Neurodegeneration and Coronary Artery Disease. *J. Affect. Disord.* **2010**, *125*, 287–294.

9. Hussain, M.; Kumar, P.; Khan, S.; Gordon, D.; Khan, S. Similarities Between Depression and Neurodegenerative Diseases: Pathophysiology, Challenges in Diagnosis and Treatment Options. *Cureus* **2020**, *12*, e11613.

10. Mahgoub, N.; Alexopoulos, G.S. Amyloid Hypothesis: Is There a Role for Antiamyloid Treatment in Late-Life Depression? *Am J. Geriatr. Psychiatry* **2016**, *24*, 239–247.

11. Harrington, K.D.; Lim, Y.Y.; Gould, E.; Maruff, P. Amyloid-Beta and Depression in Healthy Older Adults: A Systematic Review. *Aust. N. Z. J. Psychiatry* **2015**, *49*, 36–46.

12. van Dyck, C. H.; O'Dell, R. S.; Mecca, A. P. Amyloid-Associated Depression—or Not? *Biol. Psychiatry* **2021**, *89*, 737–738.

13. Krell-Roesch, J.; Lowe, V.J.; Neureiter, J.; Pink, A.; Roberts, R.O.; Mielke, M.M.; Vemuri, P.; Stokin, G.B.; Christianson, T.J.; Jack, C.R.; et al. Depressive and Anxiety Symptoms and Cortical Amyloid Deposition among Cognitively Normal Elderly Persons: The Mayo Clinic Study of Aging. *Int. Psychogeriatr.* **2018**, *30*, 245–251.

14. Kumar A, Kepe V, Barrio JR, et al. Protein Binding in Patients With Late-Life Depression. *Arch. Gen. Psychiatry* **2011**, *68*, 1143–1150.

15. Wu K.Y.; Hsiao I.T.; Chen C.S.; Chen C.H.; Hsieh C.J.; Wai Y.Y.; Chang C.J.; Tseng H.J.; Yen T.C.; Liu C.Y.; Lin K.J. Increased brain amyloid deposition in patients with a lifetime history of major depression: evidenced on 18F-florbetapir (AV-45/Amyvid) positron emission tomography. *Eur. J. Nucl. Med. Mol. Imaging* **2014**, *41*, 714–722.

16. Mackin, R. S. Mackin, R.S.; Insel, P.S.; Landau, S.; Bickford, D.; Morin, R.; Rhodes, E.; Tosun, D.; Rosen, H.J.; Butters, M.; Aisen, P.; et al. Late-Life Depression Is Associated With Reduced Cortical Amyloid Burden: Findings From the Alzheimer's Disease Neuroimaging Initiative Depression Project. *Biol. Psychiatry* **2012**, *89*, 757–765.

17. Wu, K.-Y. *et al.* Decreased Cerebral Amyloid-β Depositions in Patients With a Lifetime History of Major Depression With Suspected Non-Alzheimer Pathophysiology. *Front. Aging Neurosci.* 2022, *14*, 857940.

18. Chen, J.; Bai, S.-J.; Li, W.; Zhou, C.; Zheng, P.; Fang, L.; Wang, H.; Liu, Y.; Xie, P. Urinary Biomarker Panel for Diagnosing Patients with Depression and Anxiety Disorders. *Transl. Psychiatry* **2018**, *8*, 192.

19. Papakostas, G. I.; Shelton R.C.; Kinrys G.; Henry M.E.; Bakow B.R.; Lipkin S.H.; Pi B.; Thurmond L; Bilello J.A. Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: a pilot and replication study. *Mol. Psychiatry* **2013**, *18*, 332–339.

20. Lopresti, A.L.; Maker, G.L.; Hood, S.D.; Drummond, P.D. A Review of Peripheral Biomarkers in Major Depression: The Potential of Inflammatory and Oxidative Stress Biomarkers. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2014**, *48*, 102–111.

21. Carvalho, A.F.; Solmi, M.; Sanches, M.; Machado, M.O.; Stubbs, B.; Ajnakina, O.; Sherman, C.; Sun, Y.R.; Liu, C.S.; Brunoni, A.R.; et al. Evidence-Based Umbrella Review of 162 Peripheral Biomarkers for Major Mental Disorders. *Transl. Psychiatry* **2020**, *10*, 152.

22. Sheehan, D.V.; Lecrubier, Y.; Sheehan, K.H.; Amorim, P.; Janavs, J.; Weiller, E.; Hergueta, T.; Baker, R.; Dunbar, G.C. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* **1998**, *59* (Suppl. 20), 22–33.

23. Beck, A.T.; Ward, C.H.; Mendelson, M.; Mock, J.; Erbaugh, J. An Inventory for Measuring Depression. Arch. Gen. Psychiatry **1961**, *4*, 561–571.

24. Hamilton, M. A Rating Scale for Depression. *J. Neurol. Neurosurg. Psychiatry* **1960**, *23*, 56–62.

25. Thompson, E. Hamilton Rating Scale for Anxiety (HAM-A). *Occup. Med.* **2015**, *65*, 601.

12. Oświadczenia współautorów

12.1 Informacja o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu (praca przeglądowa)

Aleksander Nobis, Daniel Zalewski, Napoleon Waszkiewicz: *Peripheral Markers of Depression*. Journal of Clinical Medicine 2020. 9 (12) 3793. Doi: 10.3390/jcm9123793

Imię i nazwisko współautora	Charakter udziału	Procentowy wkład
doktorant – lek. Aleksander Nobis	analiza dostępnych materiałów źródłowych, przygotowanie manuskryptu, przygotowanie tabel i rycin wchodzących w skład manuskryptu	85%
lek. Daniel Zalewski	korekta manuskryptu	5%
prof. dr hab. n. med. Napoleon Waszkiewicz	stworzenie koncepcji pracy, konsultacja merytoryczna, korekta manuskryptu	10%

Oświadczam, że wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej lek. Aleksandra Nobisa.

Podpis doktoranta

lek. Daniel Zalewski
Klinika Psychiatrii
Uniwersytetu Medycznego w Białymstoku
ul. M. Wołodyjowskiego 2
15-272 Białystok

Białystok, 30.06.2023

OŚWIADCZENIE

Oświadczam, iż mój udział w publikacji:

Aleksander Nobis, Daniel Zalewski, Napoleon Waszkiewicz: *Peripheral Markers of Depression.* Journal of Clinical Medicine 2020. 9 (12) 3793. Doi: 10.3390/jcm9123793, wchodzącej w skład rozprawy doktorskiej lek. Aleksandra Nobisa, wynoszący 5%, polegał na korekcie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie przez lek. Aleksandra Nobisa powyższej publikacji w postępowaniu o nadanie stopnia doktora nauk medycznych.

Prof. dr hab. n. med. Napoleon Waszkiewicz
Klinika Psychiatrii
Uniwersytetu Medycznego w Białymstoku
ul. M. Wołodyjowskiego 2
15-272 Białystok

OŚWIADCZENIE

Oświadczam, iż mój udział w publikacji:

Aleksander Nobis, Daniel Zalewski, Napoleon Waszkiewicz: *Peripheral Markers of Depression*. Journal of Clinical Medicine 2020. 9 (12) 3793. Doi: 10.3390/jcm9123793, wchodzącej w skład rozprawy doktorskiej lek. Aleksandra Nobisa, wynoszący 10%, polegał na stworzeniu koncepcji pracy, konsultacji merytorycznej i korekcie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie przez lek. Aleksandra Nobisa powyższej publikacji w postępowaniu o nadanie stopnia doktora nauk medycznych.

KIEROWNIK
Kliniki Psychiatrii

Prof. dr hab. n. med. Napoleon Waszkiewicz

12.2. Informacja o charakterze udziału współautorów w publikacjach wraz z szacunkowym określeniem procentowego wkładu (praca oryginalna)

Aleksander Nobis, Daniel Zalewski, Eliza Samaryn, Mateusz Maciejczyk, Anna Zalewska, Napoleon Waszkiewicz: *Urine 3-Nitrotyrosine and Serum HDL as Potential Biomarkers of Depression.* Journal of Clinical Medicine 2023. 12 (1) 377. Doi: 10.3390/jcm12010377

Imię i nazwisko współautora	*Charakter udziału*	*Procentowy wkład*
doktorant – lek. Aleksander Nobis	Udział w planowaniu eksperymentów, przeprowadzanie eksperymentów prezentowanych w pracy, opracowanie i analiza wyników, analiza statystyczna, przygotowanie manuskryptu, przygotowanie tabel i rycin wchodzących w skład manuskryptu	61%
lek. Daniel Zalewski	Pomoc przy rekrutowaniu pacjentów do badania i tworzeniu bazy danych	10%
lek. Eliza Samaryn	Pomoc przy rekrutowaniu pacjentów do badania i tworzeniu bazy danych	10%
dr hab. n. med. Mateusz Maciejczyk	Przeprowadzenie oznaczeń biochemicznych, konsultacja merytoryczna	5%
prof. dr hab. n. med. Anna Zalewska	Współuczestnictwo w przeprowadzeniu oznaczeń biochemicznych, konsultacja merytoryczna	5%
prof. dr hab. n. med. Napoleon Waszkiewicz	stworzenie koncepcji pracy, nadzór nad powstawaniem pracy, konsultacja merytoryczna, korekta manuskryptu	9%

Oświadczam, że wszyscy współautorzy wyrazili zgodę na wykorzystanie powyższej publikacji w pracy doktorskiej lek. Aleksandra Nobisa.

Podpis doktoranta

Białystok, 30.06.2023

lek. Daniel Zalewski
Klinika Psychiatrii
Uniwersytetu Medycznego w Białymstoku
ul. M. Wołodyjowskiego 2
15-272 Białystok

OŚWIADCZENIE

Oświadczam, iż mój udział w publikacji:

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Jednocześnie wyrażam zgodę na wykorzystanie przez lek. Aleksandra Nobisa powyższej publikacji w postępowaniu o nadanie stopnia doktora nauk medycznych.

Białystok, 30.06.2023

lek. Eliza Samaryn
Klinika Psychiatrii
Uniwersytetu Medycznego w Białymstoku
ul. M. Wołodyjowskiego 2
15-272 Białystok

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Eliza Samaryn
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lekarz
3553767

Białystok, 30.06.2023

dr hab. n. med. Mateusz Maciejczyk
Zakład Higieny, Epidemiologii i Ergonomii
Uniwersytetu Medycznego w Białymstoku
ul. Mickiewicza 2c
15-022 Białystok

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prof. dr hab. n. med. Anna Zalewska
Zakład Stomatologii Zachowawczej
Uniwersytetu Medycznego w Białymstoku
ul. M. Skłodowskiej-Curie 24A
15-276 Białystok

OŚWIADCZENIE

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Prof. dr hab. Anna Zalewska
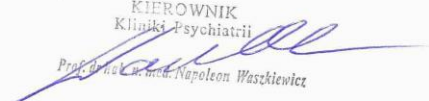specjalista stomatologii dziecięcej
8897157

Białystok, 30.06.2023

prof. dr hab. n. med. Napoleon Waszkiewicz
Klinika Psychiatrii
Uniwersytetu Medycznego w Białymstoku
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KIEROWNIK
Kliniki Psychiatrii
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