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EDITORIAL

Mavridis' atrophy in Parkinson's disease-five years later: Future perspectives

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Abstract

Mavridis' atrophy (MA) is called the human nucleus accumbens (NA) atrophy in Parkinson's disease (PD). MA begins in early-stage PD patients and is correlated with psychiatric symptoms that occur in PD, mainly apathy and impulsive behavior. It is also associated with cognitive PD symptoms. Purpose of this editorial was to discuss the future perspectives of MA as a pathological and imaging finding. MA is obviously part of the degeneration of the dopaminergic nigrostriatal system that occurs in PD and this also explains the fact that MA precedes clinical phenotype. But does the human NA follow the same pattern of degeneration? It would be quite interesting to have a post-mortem pathological study focused on the NA of parkinsonic individuals. Further questions that remain to be answered are whether all parkinsonics suffer MA and whether this phenomenon is also associated with motor PD symptoms. MA as an imaging finding could be a risk factor for the expression and/or severity of specific PD symptoms. It has therefore to be tested whether the presence of MA is related, for example, with the expression and/or severity of motor PD symptoms and whether the severity of MA affects the severity of specific psychiatric symptoms (apathy, compulsive behavior) of parkinsonic individuals. Such clinical studies, that could provide answers to these vital questions, can be easily preformed given the high frequency of PD in modern populations. Future research efforts are mandatory to enrich our knowledge of MA, namely its underlying mechanisms, its pathological features and its clinical consequences.

Key words: Parkinson's disease; Mavridis' atrophy; Nucleus accumbens; Neuroimaging; Neuropathology; Substantia nigra

Core tip: Mavridis' atrophy (MA) is the nucleus accumbens atrophy in Parkinson's disease (PD). MA begins in early-stage PD patients and is correlated with psychiatric and cognitive PD symptoms. MA is obviously part of the dopaminergic nigrostriatal degeneration that occurs in PD. It would be interesting to have a post-mortem pathological study focused on the nucleus accumbens of parkinsonic individuals. MA as an imaging finding could be a risk factor for the expression and/or

severity of specific symptoms. Thus it has to be tested whether the presence of MA is related, for example, with the expression and/or severity of motor PD symptoms.

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MAVRIDIS' ATROPHY

Parkinson's disease (PD), a common neurodegenerative disorder, is predominantly a disorder of basal ganglia, which are a group of nuclei situated deep and centrally at the base of forebrain and their main components are the striatum (caudate nucleus, putamen, nucleus accumbens), the globus pallidus, the substantia nigra (SN) and subthalamic nucleus[1-3].

The human nucleus accumbens (NA) is a major part of the ventral striatum. Connected to the limbic and extrapyramidal motor system, it has a modulating function in the amygdala-basal ganglia-prefrontal cortex circuit and is considered as the neural interface between motivation and action (limbic-motor interface). It is a modulator of the reward circuits (major pleasure center) of the human brain and thus involved in several cognitive, emotional and psychomotor functions, as well as in some of the commonest neurological and psychiatric disorders, including PD[3].

Mavridis' atrophy (MA), discovered five years ago as an imaging finding, is called the human NA atrophy in PD[4-10]. Several new data regarding MA were published during the last few years. More specifically, MA, confirmed by recent clinical studies, begins in early-stage PD patients and is correlated with psychiatric symptoms that occur in PD, mainly apathy and impulsive behavior. The MA phenomenon is also associated with cognitive PD symptoms[10]. Purpose of this editorial was to discuss the future perspectives of MA as a pathological and imaging finding.

FUTURE PERSPECTIVES

Parkinson's pathology and Mavridis' atrophy

The recognized neuropathological findings in PD are: (1) The degeneration which leads to cell death of the pigmented neurons in the pars compacta region of the SN that produce the neurotransmitter dopamine. The loss of dopaminergic neurons occurs most prominently in the ventral lateral SN. Approximately 70% of these neurons are lost before the motor signs of PD emerge[11]; and (2) The presence of Lewy bodies (cytoplasmic inclusions) in perikarya and Lewy neuritis in the neurons which result in premature cell death of the affected neurons. Their prevalence increases with age, but they are specific to PD and are found in some cases of synucleinopathies and other disorders[11,12].

PD belongs to a group of neurodegenerative disorders called a-synucleinopathies which are characterized by the intracellular presence of a neuronal protein called α-synuclein, the major component of Lewy bodies (LBs). Primary α-synucleinopathies include PD, dementia with Lewy bodies and multiple system atrophy, where the α-synuclein deposition occurs in oligodendrocytes rather than neurons. While all α-synucleinopathies are characterized by α-synuclein aggregates with similar posttranslational modifications and lipid associations, the cell type involved, their location and their association with other protein depositions vary substantially[13]. A-synuclein aggregation in the form of LBs has been also reported in neurodegenerative diseases that are not synucleinopathies, specifically in Alzheimer's disease, Pick's disease and in corticobasal degeneration[14,15]. In the last two cases the LB are detected within the cytoplasm of the characteristic balloon neurons[15].

PD is morphologically featured not only by the degeneration of the dopaminergic nigrostriatal system, responsible for the motor deficits, but also by multifocal involvement of the central, peripheral and autonomic nervous system and other organs associated with widespread occurrence of Lewy bodies and dystrophic Lewy neurites. This results from deposition of abnormal α-synuclein, the major component of Lewy bodies and the main protein marker of PD and of other synucleinopathies[16,17].

Regarding the pathological changes that characterize MA, it seems obvious this is part of the degeneration of the dopaminergic nigrostriatal system and this also explains the fact that MA precedes clinical phenotype. It should be noted here that the SN is one of the very few areas of the human brain which are connected to the NA with both afferent and efferent fibers[3,6]. But does the human NA follow the same pattern of degeneration? Do Lewy bodies present in the NA neurons of parkinsonic patients? Probably yes. But is this presence related with the process of MA? It would be quite interesting to have a post-mortem pathological study focused on the NA of parkinsonic individuals. Further questions that remain to be answered are whether all parkinsonics suffer MA and whether MA is also associated with motor PD symptoms.

Parkinson's imaging and MA

Until recently, conventional magnetic resonance imaging was usually negative in PD or showed nonspecific findings. Recent developments in structural MRI, such as relaxometry, magnetization transfer and neuromelanin imaging, have demonstrated improved contrast and enabled more accurate visualization of deep brain nuclei, in particular the SN, and cortex[18,19]. Meanwhile, diffusion imaging has provided useful biomarkers of SN degeneration, showing reduced anisotropy and anatomical connectivity with the

striatum and thalamus[18,20]. The most well-developed MRI markers in PD include diffusion imaging and iron load using T2/T2* relaxometry techniques. Other biomarkers such as susceptibility-weighted imaging for iron load, magnetization transfer and ultra-high-field MRI have shown great potential[19]. These advances in structural imaging are complemented by findings of magnetic resonance spectroscopy on brain metabolism and resting-state functional MRI on functional connectivity[18]. Using resting-state functional MRI, for example, it has been found that the presence of apathy, one of the most common neuropsychiatric symptoms in PD affecting 23%-70% of patients, is associated with functional connectivity reductions in frontostriatal circuits, predominating in the left hemisphere and mainly involving its limbic components[21]. It has also to be mentioned that brain perfusion can be assessed using non-contrast-agent techniques such as arterial spin labeling and that spectroscopy gives access to metabolites' concentrations[19].

Regarding the MA as an MRI finding in PD, it is time to evaluate the usefulness of its observation in clinical practice. It could be a risk factor for the expression and/or severity of specific PD symptoms. Thus it has to be tested whether the presence of MA is related, for example, with the expression and/or severity of motor PD symptoms and whether the severity of MA affects the severity of specific psychiatric symptoms (apathy, compulsive behavior) of parkinsonic individuals. Such clinical studies, that could provide answers to these vital questions, can be easily preformed given the simplicity of their methodology and the high frequency of PD in modern populations. Current MRI viewing software can be very helpful in identifying and even quantifying NA shrinkage. Finally, it would be also interesting to study the NA functional imaging of parkinsonic patients.

Finally, hypothesizing which type of motor symptoms could be linked to MA, we should mention hypokinetic and akinetic symptoms, because these have been suggested as some of the possible clinical consequences of MA[9]. But could the early identification of MA using neuroimaging techniques serve to prevent the disability associated with PD? Given that we are currently just seeing the "peak" of the "iceberg" called "MA"[10], we cannot be sure yet. It is highly probable that it is expected to help in setting diagnosis in a quite early or even preclinical stage of the disease, since MA is already present in early-stage PD[8]. And this should force us to focus on prevention and treatment efforts in such stages that could, if not prevent, at least delay the progression of PD-related disability. And this could be a significant step forward.

CONCLUSION

In conclusion, MA is an interesting new finding in PD, confirmed by recent clinical data. It is for sure that further research efforts are mandatory to enrich our knowledge of MA, namely its underlying mechanisms, its pathological features and its clinical consequences. We believe for example that MA is associated with motor PD symptoms, an interesting hypothesis that remains to be confirmed by clinical studies. So, future research should be directed to the clinical usefulness of MA and its relative applications.

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REVIEW

Targeting remyelination treatment for multiple sclerosis

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Abstract

Since disability in multiple sclerosis (MS) is a product of neurodegeneration and deficient remyelination, the ability to enhance neuroregeneration and myelin regeneration in MS is an enticing goal for MS drug development. In particular, remyelination treatments could promote return of neurological function and also prevent further axonal loss and neurodegeneration in MS due to trophic effects of myelin. The study of remyelination has advanced dramatically in the last several years such that a number of pathways inhibiting remyelination have been discovered, including those involving LINGO-1, Notch-1, hyaluronan, retinoid X receptor, and wnt/ß-catenin. Other approaches such as high throughput drug screening for remyelination drugs have caught fire, with identification of dozens of known drugs with oligodendrocyte maturation stimulatory effects. Several drugs identified through screens and other mechanisms are in the process of being further evaluated for remyelination in MS and MS models. We discuss the potential molecular targets and the variety of mechanisms towards drug identification and development in remyelination for MS.

Key words: Multiple sclerosis; Myelin; Remyelination; Oligodendrocyte; Repurposing; Treatment

Core tip: Over the last several years numerous remyelination pathways important to multiple sclerosis (MS) have been identified, including those of LINGO-1, hyaluronan, Notch-1, retinoid X receptor receptor, and wnt/ß-catenin. Newer discoveries include the pathways involving Chemokine (C-X-C Motif) ligand 12/C-X-C chemokine receptor type 4 and G protein-coupled receptor 17, and the involvement of Endothelin-1 in the Notch pathway. High-throughput screens have identified multiple antimuscarinic drugs with good remyelination. Also identified by screens, clemastine, with similar antimuscarinic but also antihistamine effects, may be useful in remyelination in MS. Drug repurposing, through screens or more serendipitously, has found that many drugs could enhance remyelination, including benztropine, clemastine, quetiapine, fasudil, olesoxime, and ibudilast, among others.

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INTRODUCTION

Multiple sclerosis (MS) is a debilitating disease of the central nervous system (CNS) that affects nearly 2.5

million people worldwide and is characterized by the predominant presentation in young women compared to men[1]. It manifests through an autoimmune inflammatory response which damages the protective myelin coating on axons, leading to disrupted neurological functioning[1]. Continued relapses can lead to irreversible damage within the CNS, driving clinical deterioration[2]. The MS spectrum ranges from 50%-85% of people initially diagnosed with MS beginning with the relapsing-remitting form of MS (RRMS); after approximately 10-20 years, most patients with RRMS transition to secondary progressive MS which is characterized by irreversible neurological decline[3]. MS takes a toll both physically and mentally within the patients, leading to a disease that requires management entailing high financial costs to both patients and health care systems.

The basis of neurological disability arises from neurodegeneration, defects in myelination, and continued inflammation[1]. Neurodegeneration develops over time in MS patients as a consequence of autoimmune inflammation and incomplete remyelination. Since myelin is attacked by autoimmune inflammation, damage can be primarily demyelination with axonal preservation, and this alone can cause neurological dysfunction unless repaired.

No drugs are currently in use to help prevent neurodegeneration or poor remyelination in MS. Drugs currently approved by the Food and Drug Administration (FDA) for MS treatment are immunomodulators/immunosuppressors that prevent or limit inflammation from occurring but do not directly repair damage already incurred on axons and myelin. Understanding that neurodegeneration and poor remyelination is the primary source of disability in MS, there is avoid in MS treatments aimed at remyelination in MS. This paper outlines the search for remyelination enhancing agents through drug repurposing and high throughput screens aimed at isolating an agent that removes the roadblocks to remyelination in the MS CNS.

NATURAL REMYELINATION IN MS

Remyelination can be a natural reparative mechanism in MS. Remyelination appears to require activation of oligodendrocyte progenitor cells (OPCs), recruitment of OPCs to lesions, and cellular differentiation of OPCS to become myelin-producing oligodendrocytes[4]. Remyelination occurs in the brains of some MS patients though not as complete as to allow for full return of normal function. In one post-mortem study, MS white matter lesions were 47% remyelinated on average and 22% of them were found to be fully remyelinated. This points to the existence of remyelination mechanisms even during late stages of disease[5]. However, this and other data indicate that remyelination is incomplete in the majority of cases.

It cannot be overstated that remyelination should lead to a host of benefits to the MS patient. Remyelination can strengthen function by reestablishing electrical communication between neurons and prevent further neurodegeneration through trophic support of neurons and axons[1]. Research targeting remyelination drug therapy requires an understanding of the reasons why natural remyelination eventually fails in patients with MS.

APPROACHES IN REMYELINATION DRUG DEVELOPMENT

The timeline for taking a drug from the laboratory to the consumer market is long and costly, creating a situation of diminishing returns and leading to the focus on the repurposing of existing, proven drugs. In general, novel drugs experience 1-6 years of preclinical development, 6-11 years of clinical trials, and then 0.6-2 years for FDA approval, for a total of 7.6-19 years. Sometimes drug development occurs rapidly, as was the case of natalizumab, first identified as a potential MS treatment in 1999[6] and winning FDA approval in 2004.

Drug repurposing (also referred to as repositioning or re-profiling) utilizes existing drugs for the treatment of a disease that was not the drug's original target. These drugs have already passed through pre-clinical and clinical stages of testing examining safety profiles and tolerability, which streamlines the process to finding treatments[7]. For example, metformin, a commonly prescribed drug for diabetes, may be suggested as a chemotherapeutic agent given its association with decreased mortality in cancer patients[8]. The antimalarial drug chloroquine may have important anticancer properties[9]. First introduced in 1957 for its antiemetic and sedative properties, thalidomide has since been repurposed for multiple myeloma treatment[10]. Interestingly, dimethylfumarate was originally in use since 1959 for psoriasis[11], was repurposed for MS treatment in 2004, went straight to phase 2 trials, and recently won FDA approval for MS treatment in 2013. Thus, while there was a long delay in repurposing dimethylfumarate, FDA approval of repurposed drugs like dimethy fumarate can occur relatively rapidly after selection for MS clinical trials.

This method of borrowing from both similar and dramatically different diseases' existing drugs creates an environment where the costly overhead of research and development and clinical trials can be eliminated. Drug repurposing can be implemented in searching for a remyelination-enhancing agent in MS even many years after they are brought to market for other applications. Since many candidate drugs already exist for repurposing, high throughput screens should be particularly amenable to drug discovery. Ultimately, repurposing provides a faster and more productive way to search for and isolate a viable remyelinating agent for MS.

Though more difficult, it may also be possible to devise novel drugs that attack specific pathways involved in remyelination in MS. High throughput screens could

Table 1 Known pathways affecting remyelination in multiple sclerosis

Pathway	Potential protein targets	Drugs	Ref.
Hyaluronan	TLR2	TLR2 Ab (OPN-305)	[28]
	Hyaluronidase	Vcpal	[28,30]
Notch-1	Notch-1	(pan) BMS-906024	[14,15,17,19]
	Jagged-1	-	[14]
	Endothelin-1	PD142,893, sitaxentan, ambrisentan, atrasentan, BQ-123, zibotentan, bosentan, macitentan, tezosentan	[17]
	γ-secretase	MW167, LY450139	[93]
Retinoid X receptor	RXR-γ	Bexarotene, IRX4204	[31]
Wnt/ß-catenin	ß-catenin	PKF118-744, CGP049090, PKF118-310, XTM000990, BC21, PKF115-584, PNU-74654	[21,22]
	Tankyrases 1-2	XAV939, IWR1, JW74, JW55	[57]
	GSK3ß	SB216763	[20]
LINGO-1	LINGO-1	Anti-LINGO-1 Ab	[23-25]
CXCL12/CXCR4	CXCR7	CCX771	[37,38]
	CXCR4	AMD3100	[37,38]
GPR17	GPR17	Unnamed	Omeros

TLR2: Toll-like-receptor 2; GPR17: G protein-coupled receptor 17; CXCL4: C-X-C chemokine receptor type 4; CXCL12: Chemokine (C-X-C Motif) ligand 12.

be designed around specific components of the identified pathway as a surrogate assay for remyelination. As described below, several pathways have been identified that control remyelination in MS and relevant animal models. With characterization of the molecular components of these pathways, it may be possible to design novel drugs or repurpose old drugs targeting these pathways to enhance remyelination in MS. In a review of the literature, both novel drug discovery and existing drug repurposing are being utilized in drug development in MS.

KNOWN REMYELINATION PATHWAYS IN MS

One of the most prominent issues with inhibited remyelination is that recruited progenitors fail to mature after they are recruited to the lesion site[12]. Multiple mechanisms are proposed for the blockade of OPC maturation, including pathways involving Notch-1, Wnt, LINGO-1, hyaluronan, and Retinoid X receptor (RXR) receptor (see Table 1). One of the first pathways to be identified was involving Notch-1, which responds to a broad array of ligands including Jagged1, Delta, Contactin, and Endothelin-1[13-17]. Originally increased Jagged1 expression was noted in reactive astrocytes stimulated with TGF-ß1[14]. Borders of acute MS lesions exhibited increased expression of Jagged1, Notch-1, and inhibitory basic helix-loop-helix protein, Hes5, suggesting the presence of active Jagged1/Notch-1 signaling.

However, followup *in vivo* work was initially more contradictory, with conditional deletion of Notch-1 in PLP+ oligodendrocytes having no effect on remyelination in the cuprizone model of demyelination/remyelination[18]. Because PLP+ oligodendrocytes may be too far along in maturation to respond to Notch-1 signaling, conditional deletion of Notch-1 in CNP+ oligodendrocytes was performed, and this did in fact show precocious oligodendrocyte maturation[19]. Similarly, conditional deletion of Notch-1 in Olig2 oligodendrocytes also promoted premature oligodendrocyte maturation[19]. Remyelination was more extensive after lysolecithin demyelination in these mice as well. More recently, Endothelin-1 expression by astrocytes appears to limit oligodendrocyte through Notch-1 signaling in animal models of remyelination[17]. However, contactin is increased in MS lesions and induces myelin-associated glycoprotein (MAG) upregulation after Notch-1 stimulation[15], suggesting different opposing effects of Notch-1 on oligodendrocyte maturation. If the inhibitory effect of Notch-1 can be better characterized, there may be an opportunity to target this pathway to enhance remyelination in MS, as inhibitors to Notch, Endothelin-1 and gamma-secretase exist and have been studied in humans for other conditions (Table 1).

The canonical wnt signaling pathway has also been identified for remyelination purposes[20-22]. Although the developmental role of the wnt pathway in oligodendrocyte maturation has been known for some time, the involvement of the wnt pathway was more recently uncovered in a mouse lysolecithin injection model by in situ screens of 1040 transcription factors[21]. Three additional murine multiple sclerosis models were used to confirm the role of the wnt pathway in remyelination, including lysolecithin injection, cuprizone intoxication, and ethidium bromide injection models. TCF4 a major transcription factor involved in wnt signaling, is expressed in OPCs in demyelinated lesions. A transgenic mouse expressing dominant negative TCF4 exhibited normal OPC development but grossly impaired oligodendrocyte maturation[22]. Dominant active ß-catenin in Olg2+ cells showed decreased mature oligodendrocytes in spite of normal oligodendrocyte numbers, as well as evidence of reduced myelination in development[21]. Olig1+ specific knockout of ß-catenin also induced premature oligodendrocyte development[22]. Since Wnt pathway activation and protein expression was observed in MS lesions[21], it remains possible that the wnt pathway controls remyelination in MS.

There are multiple drugs identified that target

wnt and ß-catenin and can be assessed for effects on remyelination *in vivo*. Other targets in the wnt/ß-catenin cascade, including disheveled, axin, and porcupine, could be involved in limited OPC maturation. There are many small molecular weight drugs in clinical trials or approved for human use that modulate the functions of these proteins and wnt signaling as well, including sulindac (disheveled), bosutinib (Src kinase inhibitor) and imatinib (tyrosine kinase inhibitor) (Table 1).

Leucine rich repeat and Ig domain containing 1 (or LINGO-1) has also been shown to limit oligodendrocyte maturation and remyelination[23-25]. Upregulation and downregulation of LINGO-1 expression restricts and enhances features of oligodendrocyte maturation *in vitro*[23-25]. Functional blockade of LINGO-1 through blocking antibodies or dominant negative LINGO-1 enhances myelin sheet formation, induction of MBP expression, and myelination *in vitro*[23-25]. The repressive effect of LINGO-1 appears to work through downstream activation of a rho kinase (ROCK)[25]. *In vivo* overexpression of LINGO-1 reduces cord myelination[26]. Conversely, LINGO-1 KO mice show increased myelination in development and oligodendrocyte cultures contain an increased percentage of mature oligodendrocytes[25]. Antibody blockade of LINGO-1 enhances remyelination in EAE when given after peak disease activity, indicating an effect on remyelination processes rather than immune functions most likely[23]. Remyelination is also enhanced by anti-LINGO-1 antibody treatment in other models, including the lysophosphatidylcholine injection and cuprizone models[24]. Clearly, there is great potential for anti-LINGO-1 treatment in MS and phase 1 clinical trials are now underway (NCT01052506 and NCT01244139) (Table 1).

The glycosaminoglycan hyaluronan (HA) also inhibits OPC maturation[27,28]. Our group found that HA blocked OPC maturation in a dose-dependent manner[28]. Because specific Toll-Like-Receptor 2 (TLR2) agonists blocked OPC maturation, HA was suspected to act through TLR2 on oligodendrocytes. This suspicion was confirmed when TLR2-blocking antibodies ablated the effects of HA on OPC maturation. The downstream signaling of TLR2 was also implicated when small molecular weight inhibitors of MyD88 and IRAK1/4 also ablated the effects of HA *in vitro*. When lysolecithin and HA were injected into TLR2-null mice, enhanced remyelination occurred compared to wild-type mice. These findings indicate that HA acts on TLR2 to inhibit OPC maturation.

Our work further implicated hyaluronidase in the hyaluronan pathway. Our group suspected that high molecular weight (HMW) HA must be converted to low molecular weight (LMW) HA in order to act on TLR2, since both LMW and HMW HA block OPC maturation though only LMW is known to stimulate TLR2[28,29]. Only complete degradation of HMW HA by both hyaluronidase and ß-glucuronidase neutralized the effects of HA on OPCs by completely degrading all sources of HA. Ascorbate 6-hexadecanoate (Vcpal), a hyaluronidase inhibitor, cultured with OPCs and HMW HA allowed OPC maturation to proceed normally by limiting the conversion of HMW HA to LMW HA[28]. This effect of Vcpal was confirmed *in vivo*[30]. Based on these exciting findings, hyaluronidase inhibition should be further evaluated for remyelination effects in MS (Table 1).

Retinoid X receptor gamma (RXR-γ) has been implicated as a positive regulator in CNS remyelination[31]. RXR-γ is a nuclear receptor that dimerizes with other receptors, including retinoic acid receptors, thyroid hormone receptors, vitamin D receptors, and peroxisome proliferator activator receptors to regulate cell differentiation, proliferation, and apoptosis[32]. In MS, RXR-γ expression increases in the nuclear component of OPCs in active lesion borders but is lowered in chronic inactive lesions, suggesting RXR-γ plays a positive role in remyelination. RXR-γ is also strongly upregulated after demyelination from lysolecithin injection. Knockdown of RXR-γ expression in OPCs promotes simple undifferentiated cellular morphology compared to controls. *In vitro* testing of RXR-selective antagonists (HX531 and PA452) with OPCs reduced MBP expression. In contrast, 9-*cis*-retinoic acid, an RXR activator, increased the number of MBP+ membrane sheets in culture. *In vivo* testing showed an increased level of CC1+ differentiated oligodendrocytes and thicker myelin sheaths after 9-*cis*-retinoic acid treatment[31].

In mouse models of Alzheimer's disease, the RXR agonist bexarotene improved cognitive functioning and decreased amyloid-β plaque burden[33]. Bexarotene also has positive effects in shizophrenia[34] and cutaneous T cell lymphoma[35]. Though bexarotene nonspecifically acts on all retinoid X receptors, testing in MS patients can confirm whether bexarotene may be successful in promoting remyelination in MS. Other RXR agonists including IRX4204 may be immediately useful in clinical trials of remyelination in MS, although more preclinical work needs to be performed (Table 1)[36].

Recently, certain chemokines have been identified that modulate remyelination, although effects on inflammation are likely also involved. CXCL12 promotes remyelination by acting on the receptor CXCR4 on OPCs. The recently discovered scavenge receptor for CXCL12, CXCR7 limits the availability of CXCL12 to act on CXCR4[37]. During demyelination in cuprizone-fed animals, both receptors and CXCL12 were elevated above levels in control animals[38-41]. During remyelination phase, CXCR7 expression returns to normal while CXCR4 and CXCL12 remain elevated. CXCR7 appears to regulate the availability of extracellular CXCL12. When CCX771, a CXCR7 antagonist, was given to animals during weeks three to six (remyelination phase) of a six week cuprizone-infused diet, levels of CXCL12 and ligand activated CXCR4 were elevated in the corpus callosum. Once mice were allowed to remyelinate after cessation of the cuprizone and CCX771, mice showed significantly increased numbers of GST-pi+ (mature oligodendrocyte marker) cells and increased myelin oligodendroglial

glycoprotein (MOG) expression and myelin staining. The improvement was shown to occur through CXCR4 activation by CXCL12 when a CXCR4 antagonist blocked remyelination. Increased remyelination also correlated with CXCR4 phosphorylation[38]. In EAE, CCX771 also lead to significant decrease in peak severity of disease. The antagonist ultimately preserved axonal integrity as found through diffusion tensor imaging[37]. Antagonism of CXCR4 increased disease activity while antagonism of CXCR7 significantly decreased disease severity in the mice model of experimental autoimmune neuritis based on clinical scores[41]. Thus, treatments that either enhance CXCR4 stimulation or block CXCR7 may be useful in enhancing remyelination in MS (Table 1).

The Uracil nucleotide/cysteinyl leukotriene receptor [(also known as the G-protein coupled receptor 17 (GPR17)] is known to be involved with OPC differentiation and is activated by uracil-nucleotides (UDP-sugars) and cysteinyl-leukotrienes LTC4 and LTD4[42,43]. GPR17 mRNA levels peak in conjunction with rising MBP levels in maturing OPC cultures. In morphologically mature oligodendrocytes, GPR17 expression then decreases to very low levels. Since UDP-glucose increased the number MBP expressing cells and GPR17 expression is highest in OPCs, it was initially thought that GPR17 plays a stimulatory role in the early stages of differentiation[44]. Complicating its role in oligodendrocyte biology, GPR17 also appears to play a role in OPC migration as GPR17 antagonist prevented migration[45].

Though scientists are convinced that GPR17 activation could enhance therapy for demyelinating diseases, the role of GPR17 in remyelination is accompanied by much debate because GPR17 expression and activation is also thought to arrest progenitors in a premature state. GPR17 overexpressing transgenic mice showed significant reduction in MBP and PLP1 expression. Prolonged overexpression in the transgenic mice resulted in differentiation arrest or apoptotic cell death compared to WT animals[46]. These *in vivo* data countered understanding that GPR17 plays a positive role in OPC maturation and instead supported the idea that GPR17 arrests CNS cells at a pre-myelination stage. However, efforts towards creating a safe and effective GPR17 antagonist were put into motion once the GPR17 activator MDL29951 inhibited oligodendrocyte maturation in culture[47]. As part of its G-protein coupled receptors (GPCR) program, the biopharmaceutical company Omeros significantly increased mean clinical scores using GPR17 antagonists in EAE animals. Identification and evaluation of GPR17 modulators in multiple remyelination models is needed to fully evaluate for remyelinating effects (Table 1).

Other factors also play a role in remyelination and may inhibit oligodendrocyte maturation. Chondroitin sulphate proteoglycans (CSPGs) that exist on the surface of terminally differentiated oligodendrocytes inhibit growth responses using the Rho/ROCK/LIMK cascade[48]. Klotho expression in brain decreases with age and enhances oligodendrocyte maturation as well as cognitive benefits[49]. Axonal damage can also result in the accumulation of myelin-associated inhibitors or myelin debris that inhibits OPC differentiation[50,51]. Efficient phagocytic removal of myelin debris is required for remyelination to occur[50,52]. The extent of overlap among these mechanisms is still unclear. Furthermore, drugs that modulate these additional pathways could be discovered through high throughput screens, such as with Klotho[53].

HIGH THROUGHPUT SCREENS FOR REMYELINATION INDUCING DRUGS

High throughput screening is a rapid method for identifying drugs that may be useful in treating disease. One of the difficulties in remyelination research is what screens would be useful for screening and modeling aspects of remyelination. Initial screens using zebrafish were complicated by multiple effects of drugs on OPC proliferation (olig2 counts) as well as maturation (MBP expression)[54]. With this screen several drugs were identified that increase OPC proliferation but none that enhanced maturation. Since OPC maturation is essential for remyelination and may be blocked in MS, high throughput screens utilizing OPC cultures examining markers of maturation has been identified as a more streamlined method of identifying drugs. Several drugs have been discovered using this approach recently, including benztropine[55] (Table 2).

Through use of an OPC maturation screen, benztropine was found to be a potent inducer of differentiation based on the expression of MBP and MOG *in vitro*[55]. Benztropine is a muscarinic receptor antagonist used for the treatment of Parkinson's disease and readily crosses the blood brain barrier (BBB). Cells expressed the highest level of MBP after treatment given at an immature state suggesting that the compound acts most effectively on the cells at an early stage of differentiation. In cuprizone induced demyelination and in EAE experiments, benztropine improved clinical outcomes and myelin content indicating enhancement of remyelination rather than immune effect[55].

However, benztropine is associated with dose-dependent side effects including tachycardia, paralytic ileus and urinary retention[55,56]. Although benztropine may need to be dosed at unsafe levels to be effective in MS remyelination, clinical trials in MS patients could help determine whether a safe dosage effective in promoting remyelination does indeed exist.

Based on the findings that oligodendrocytes can myelinate paraformaldehyde fixed axons as well as electron-spun nanofibers, micropillar arrays were fabricated to assess myelination drugs in a high throughput format[57] (Table 2). OPCs bound to micropillars and matured into oligodendrocytes that wrapped the micropillars. Similar to the work of Deshmukh *et al*[55], this group found a cluster of antimuscarinic compounds including benztropine that enhanced oligodendrocyte

Table 2 Drug classes identified in remyelination screens

Drug class	Compounds	Ref.
Adrenergic agonist	Methoxamine, nerepinephrine, tolaxoline, salmeterol	[55]
Dopamine antagonists	Opipramol, flupentixol, fluphenazine, trifluoperazine, perphenazine, quetiapine	[55,57]
Dopamine uptake inhibitor/dopamine agents	Vanoxerine, GBR12935, methyldopa	[55]
Histamine antagonists	Clemastine, doxylamine, clemizole	[55,57]
Adrenergic antagonist	Opipramol, trifluoperazine, Cgp-26505, tolazoline, quetiapine	[55,57]
Anticholinergics/cholinesterase reactivators	Homatropine, clemastine, benztropine, disopyramide, trospium, diacetyl-monoxime, tiotropium, oxybutynin, atropine, ipratropium, hyosamine, atropine, methy atropine, octatropine, glycpyrrolate, carbetapentane, piperildolate, bevonium, propiverine, dicyclomine, mepenzolate, trihexylphenidyl	[55,57]
Phosphodiesterase inhibitor	8-bromo cyclic GMP, IBMX, enprofylline, enoximone, rolipram	[55]
PPAR agonist	GW-1929	[55]
Ion channel blockers	Gabapentin, 8-aminobenzoic acid, disopyramide, oubain	[55]
Serotonin modulators	Brl-15572, paroxetine, clemizole, quetiapine	[55,57]
Glutamate receptor antagonist	UPF-523, l-aminodan-1,5-dicarboxylic acid	[55]
Beta-catenin inhibitor	XAV939	[55]
Retinoic acid receptor agonist	Retinoids, AM580	[55,94]
Thyroid hormone receptor agonist	T3	[55,57]
COX-2 inhibitors	Niflumic acid, flunixin	[55]
HMG-CoA reductase Inhibitor	Mevastatin, simvastatin	[55]
Rho kinase inhibitor	Ml-7, Ml-9, fasudil	[55,63,94]
Antifungal/antibacterial	Ketoconazole	[55]
Cathartic/emetic	Emetine	[55]
Opioid antagonists	Levallorphan	[55]
Glucocorticoids	Dexamethasone, hydrocortisone, budesonide, flunisolide	[94]
EGF/ErbB2 inhibitor	PD174265	[94]

PPAR: Peroxisome proliferator activator receptor. COX-2: Cyclooxygenase-2; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; EGF: Epidermal growth factor.

maturation and wrapping. Clemastine, an antihistamine compound with antimuscarinic properties, and quetiapine, an atypical antipsychotic, were also identified.

Through use of a DRG/oligodendrocyte coculture system, clemastine and benztropine were both shown to enhance myelin formation. After lysolecithin-induced demyelination, clemastine enhanced remyelination of cord lesions. Since clemastine is a safe over the counter drug (Tavist), clemastine is an exciting prospect for remyelination in MS. A phase 2 clinical trial has just begun (NCT02040298) and aims to study improvement in visual evoked potentials as well as myelin water volume and magnetization transfer ratios by MRI. Interestingly, GlaxoSmithKline is also conducting a phase 2 clinical trial (NCT01772199) largely in Europe that examines the effect of a histamine 3 receptor antagonist GSK239512 on remyelination in MS also through changes in magnetization transfer ratios. Further use of these high throughput screens may continue to identify additional targets beyond antimuscarinic (benztropine), antihistamine (clemastine), and antidopamine (quetiapine) pathways.

DRUGS IN SEARCH OF A MECHANISM

Another approach to generating drugs to help remyelinate MS brains has been a shotgun approach of generating, isolating, and identifying monoclonal antibodies with remyelinating effects. Beginning in 1987, the possibility was explored that monoclonal antibodies generated against myelin antigens might have a reparative and remyelinating effect. This work has continued to the present and has generated at least one viable antibody rHIgM22. However, a flaw in this approach is that mechanism of action is often hard to identify, as has been the case with rHIgM22.

In 2000, this line of work identified several human IgM antibodies, including rHIgM22, that enhance myelin formation from patients with Waldenstrom's macroglobinemia[58]. Once *in vivo* data confirmed its reparative properties, rHIgm22 became a very promising solution for impaired remyelination in MS because of its potency and safety. Virus-induced Theiler's murine encephalitis animals significantly reduced in clinical severity with rHIgM22 treatment at the smallest effective dose of 500 ng[59]. Volumetric measurements of spinal cord lesions revealed reduction in lesion size by 83% of all lesions. Biotinylated rHIgM22 was also able to pass the blood-brain-barrier in animals[60]. The half-life of rHIgM22 was determined to be 15.4 h and the antibody was cleared form the systems of animals within a short 48 h[61]. The short half-life and small effective dose of rHIgM22 amplified excitement for a drug with a low probability of causing adverse effects.

The mechanism through which rHIgM22 works is still unknown though *in vitro* data has identified key players working in conjunction with rHIgM22. rHIgM22 binds to the surface of oligodendrocytes though exactly what the antibody binds to is unknown[61]. In mature oligodendrocyte cultures, rHIgM22 highly co-localized with the αv integrin β3 and partially co-localized with integrin β1. Integrins are cell surface

Table 3 Repurposed drug potential for remyelination

Drug	Safety	BBB	*In vitro* effects	*In vivo* effects	MS trials	Mechanism
Quetiapine	+	+	+	+	NCT02087631	Atypical antipsychotic
Fasudil	+	NA	+	+		ROCK Inhibitor
Olesoxime	+	+	+	+	NCT01808885	Mitochondrial permeability transition pore modulator
Ibudilast	+	+	+	+	NCT01982942 NCT01910259	Phosphodiesterase PDE4 inhibitor
Simvastatin	+	+	+/-	+/-	NCT00647348	HMG-CoA reductase inhibitor
Lovastatin	+	+	+	+		HMG-CoA reductase inhibitor
Clemastine	+	+	+	+	NCT02040298	Antihistamine
IRX4204	NA	+	+	NA		Retinoid X receptor agonist
Bexarotene	+/-	+	-	-		Retinoid X receptor agonist
Benztropine	+/-	+	+	+		M1/M3 muscarinic receptor antagonist

BBB: Blood brain barrier; ROCK: Rho kinase; NA: Not available; MS: Multiple sclerosis; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A.

proteins that are involved with signaling for cell migration and differentiation. rHIgM22 also blocked oligodendrocyte apoptosis in culture based on reduction of caspase 3 and caspase 9 cleavage. Decreased MBP and MOG expression *in vitro* clarified rHIgM22's primary mechanism, which is counterintuitive. rHIgM22 primarily provides protection from cell death while also delaying differentiation. The delayed differentiation is thought to occur through growth factor mediated inhibition that keeps cells in a proliferative state[61]. Finally, it was recently found that rIgM22 effects require PDGF to increase OPC proliferation[62]. While its *in vivo* data seem very promising, more work is required to establish mechanism of action for rIgM22. Results from the ongoing rHIgM22 phase 1 clinical trial will also begin in early 2015 (Acorda Therapeutics).

REPURPOSING DRUGS FOR REMYELINATION

Discovery of remyelination drugs may be rational by dissection of known pathways, may be through drug screens, but may also be through a more serendipitous pathway. We discuss here known drugs studied for other diseases or conditions that were also assessed for effects in remyelination or MS models. While there may be others, we will discuss fasudil, quetiapine, ibudilast, and olesoxime. Simvastatin and lovastatin are possibly also useful in remyelination although they may benefit MS outcomes through other mechanisms (Table 3).

Fasudil is ROCK inhibitor used for the treatment of vascular disease[63]. ROCK-II, the downstream effector of RhoA, phosphorylates molecules responsible for actin filament regulation[64]. Fyn-1 kinase acts on the GTPase RhoA which plays a role in oligodendrocyte morphology[65]. When OPCs were cultured with fasudil and myelin protein extracts inhibitory to oligodendrocyte differentiation, oligodendrocyte differentiation proceeded more rapidly[63]. In the presence of myelin protein extracts, neonatal rat OPCs showed decreased activation of Fyn-1 and increased levels of both GTP bound RhoA and activated ROCK-II[48]. siRNA mediated gene silencing or inhibitors of the RhoA- ROCK-II pathway induced OPC differentiation in the presence of inhibitory myelin debris[63]. It is also important to note that the ROCK inhibitors Y-27632, fasudil and dimethylfasudil increased neurite outgrowth dose-dependently in neurons cultured with CSPGs[48,66]. Thus, ROCK inhibitors including fasudil may benefit MS in that these treatments may induce more remyelination as well as axonal regrowth and neuroregeneration.

Another medication that should be evaluated for repurposing for MS remyelination is quetiapine, an atypical antipsychotic approved for the treatment of schizophrenia and acute bipolar disorder[67,68]. *In vitro* data shows that quetiapine facilitates oligodendrocyte lineage development[69]. The cuprizone animal model treated with quetiapine, though analyzed for locomotive and hyperactive indicators of schizophrenia, showed increased MBP expression positively correlated with length of time the drug was administered post-cuprizone recovery. Quetiapine increased the number of mature oligodendrocytes in treated animals compared to vehicle-treated controls suggesting quetiapine enhances both oligodendrocyte maturation and survival[70]. Apart from sedative effects, this drug has been generally well tolerated in patients with Parkinson's and Alzheimer's disease but clinical trials are needed to test safety, tolerability and efficacy in patients with MS[71,72]. A phase I/II trial is underway in Canada for this purpose (NCT02087631).

Ibudilast is an anti-inflammatory drug used in the treatment of asthma and stroke in Japan. Because of its anti-inflammatory effects, Ibudilast was first investigated for effects in EAE[73]. Prophylactic ibudilast treatment ameliorated severity of EAE but did not modify disease if given after disease onset. Mechanism of action appeared to be through limiting inflammatory infiltrate with mild suppression of T cell proliferation in regional lymph nodes. However, a phase 2 trial in relapsing remitting MS showed no beneficial effect of ibudilast both in terms of relapse rate and formation of new MRI lesions in a 12 mo interval[74]. A neuroprotective effect was postulated since a significant reduction in brain atrophy and in number of persistent T1 "black holes" was observed. No analysis was possible

to differentiate neuroprotective, neuroregenerative, or remyelinative effects.

More recent data also indicate rolipram, a PDE4 phosphodiesterase inhibitor like ibudilast, promotes OPC differentiation and remyelination *in vivo*[51]. Rolipram is postulated to negate effects of myelin protein extracts on inhibiting remyelination. Unfortunately, rolipram was ineffective and poorly tolerated in phase 2 relapsing remitting MS trials[75]. Since ibudilast is more potent than rolipram in PDE4 inhibition, there is hope that ibudilast will be more effective at more tolerable dosing. Several phase 2 trials are underway in MS patients, including a NeuroNext trial (NCT01982942) and the MS-SMART trial in England (NCT01910259) that will examine amiloride, rilozole, and ibudilast. Both trials will examine magnetization transfer ratio by MRI and this may detect effects on remyelination.

A HMG-CoA reductase inhibitor used for hypercholesterolemia, simvastatin has had mixed results in remyelination studies. Simvastatin promoted elaboration and extension of OPC and oligodendrocyte processes followed by process retraction days after. Longterm simvastatin treatment of OPCs worsened cell process elaboration. Cell process retraction could however be rescued by the addition of cholesterol[76]. Simvastatin use in cuprizone models of remyelination also raised concerns about deleterious effects of simvastatin on remyelination. After demyelination by cuprizone, animals treated with simvastatin exhibited significantly less remyelination compared to controls. Simvastatin treatment appeared to maintain OPCs in an immature state with no apparent effects on overall OPC numbers. Overall, simvastatin did not promote maturation and may have even been deleterious in the cuprizone model.

Cholesterol depletion as a consequence of using simvastatin could disrupt the functioning of lipid rafts that play a role in the remyelination process[77]. Simvastatin belongs to the group of lipophilic statins that are known to reduce levels of the lipid raft marker flotillin; decreased flotillin suggests that raft-associated proteins cannot access the membranes after statin treatment[78]. Because of promising anti-inflammatory response in EAE animals[79], simvastatin did however move towards clinical trials mainly in secondary progressive MS[80]. In a 2004 study, RRMS patients were given a daily 80 mg dose of simvastatin over the course of six months. MRI analysis concluded that Gadolinium-enhancing lesion volume shrank by an average of 41% after treatment[81]. A more recent secondary progressive study on simvastatin (MS-STAT; NCT00647348) showed for the first time a dramatic benefit in clinical and MRI outcomes[82]. The average brain atrophy rate significantly decreased in the simvastatin-treated group. Expanded Disability Severity Scale scores at 24 mo were also lower than placebo (average 5.93 *vs* 6.35)[82]. At present, it is not entirely clear the mechanism through which patients on simvastatin benefited, although anti-inflammatory effects are most likely.

Another blood-brain barrier permeable lipophilic statin, lovastatin may also be considered for MS clinical trial testing. In EAE animals treated with lovastatin, MBP, proteolipid protein (PLP), MOG, and MAG expression increased compared to EAE controls though expression did not match the healthy controls[83]. Lovastatin also reduced gadolinium-enhancing lesion load in MS patients, suggesting an anti-inflammatory effect[84]. Although there is some controversy about effects on myelin formation, the statin class of drugs may provide neurologists with orally deliverable agents for secondary progressive MS and possibly for remyelination.

Olesoxime has just recently been shown to prevent progressive loss of motor function in individuals with spinal muscular atrophy and could also be considered for the treatment of MS. Olesoxime has shown promise by increasing the area of myelinated axons in mouse forebrain slice cultures by approximately 40%[85]. In the same study, healthy new born and adult mice fed olesoxime had increased numbers of oligodendrocytes in the corpus callosum along with increased numbers of myelinated axons in the region. Myelin sheath thickness increased during neonatal development when animals were treated with olesoxime. Mice were also put on a cuprizone diet to test the effects of olesoxime on the demyelination and remyelination phases in animals. At peak demyelination, treated groups had higher MBP and NF (neurofilament) content. When animals were evaluated two weeks after peak demyelination, analysis showed that proliferation was promoted during remyelination based on increased Olig2+ cell counts; a two-fold increase in myelinated axons compared to vehicle-treated animals was found as well. Animals pretreated with olesoxime food pellets were injected with lysolecithin to induce focal demyelination; in this model, expression of differentiation protein markers did not differ between the treated and untreated group though CC1+ mature oligodendrocytes were higher in number in the pretreated group. MRI analysis of the lysolecithin/olesoxime pretreated animals showed attenuation, though insignificant, of lesions in the treated group. Olesoxime is currently undergoing a phase 1b trial in MS patients as add-on therapy to the immunosuppressant interferon-beta (MSREPAIR; NCT01808885) and diffusion tensor imaging and magnetization transfer ratio will be performed to assess remyelination.

Two other drugs, minocycline and rolipram were to date unsuccessful in MS trials. Minocycline is a tetracycline antibiotic that easily crosses the blood–brain barrier and has been used to treat a variety of infections for years[86]. In a cuprizone-fed animal model, minocycline inhibited microglial activation that suppressed expression of ciliary neurotrophic transcription factor. However, the drug also decreased the number of CC1+ mature oligodendrocytes in animals[87]. In clinical trials with Rebif, minocycline use was associated with increased brain atrophy and progression and the trial was halted. Minocycline use with glatiramer showed no benefit over glatiramer alone

in MS patients as well[88].

Rolipram was originally tested for treatment of depression though not tolerated well in clinical trials. Nausea was reported as the main side effect which limited its clinical application[89,90]. When considered as a treatment option for MS, rolipram showed a dose dependent increase in MBP+ oligodendrocytes *in vitro*. After rolipram treatment, lysolecithin injected animals showed increased MAG, CNPase, and MBP expression[91]. Myelin sheaths in ethidium bromide injected animals were found to be thicker when analyzed fourteen days after lesion[51]. Positive *in vitro* and *in vivo* results propelled rolipram to a phase I/II clinical trial in a small group of MS patients. The measurement of contrast-enhancing lesions (CELs) from MRI results indicated that brain inflammatory activity actually increased with rolipram treatment. The total number of CELs per patient per month significantly increased in the treatment group. Adverse events significantly increased and exacerbations generally increased with treatment[75]. Though originally promising, rolipram dosing may not be high enough for remyelination to occur in humans. Nevertheless, rolipram may be worthy of further research efforts since both rolipram and ibudilast are phosphodiesterase inhibitors and appear to enhance remyelination in animal models.

Clearly several extant drugs could potentially be repurposed for remyelination in MS. One issue cogently raised by others in relation to the MS-STAT trial[92], is the difficulty that exists in performing required phase 3 clinical trials to validate these drugs for remyelination in MS. The patents of many of the drugs named here have expired so pharmaceutical companies are expected to have limited interest in financing expensive trials. Since no trial has actually produced positive data showing evidence of remyelination in MS, the risk is also especially high to any trial studying remyelination. Alternative funding mechanisms do not exist since NIH and other governmental agencies have no established mechanism through which a large-scale expensive trial can be performed. Furthermore, medical insurance companies may not pay for treatments only characterized by limited phase 2 trials utilizing approximately 100 patients. It remains to be seen how best to fund phase 3 trials of this sort but it is likely trials of newer and more patentable drugs will lead the way first.

CONCLUSION

Remyelination therapeutics is an emerging and exciting field in MS drug development. While it is important to remember sustained neurological deficits in MS are clearly related to both neurodegeneration as well as impaired myelination, remyelination-enhancing treatments may improve patients' function and quality of life in spite of their restricted effects. Several remyelination pathways important to MS have been identified, including those of LINGO-1, hyaluronan, Notch-1, RXR receptor, and wnt/ß-catenin. Other newer discoveries include the pathways involving CXCL12/CXCR4 and GPR17, and the involvement of Endothelin-1 in the Notch pathway. A number of known drugs with effects on these pathways can be evaluated for remyelination enhancing effects in MS, although this has yet to occur. High-throughput screens have identified multiple antimuscarinic drugs with good remyelination potential but use of at least benztropine may be problematic due to dose limiting side effects. Also identified by screens, clemastine, with similar antimuscarinic but also antihistamine effects, may be useful in remyelination in MS. Other drugs identified through other means such as rHIgM22 are in the beginning stages of clinical trials. Drug repurposing, through screens or more serendipitously, has found that many drugs could enhance remyelination, including benztropine, clemastine, quetiapine, fusadil, olesoxime, and ibudilast, among others. Many other these identified drugs are undergoing clinical trials, some with endpoints that examine remyelination. Difficulties exist in design of clinical trials to identify remyelination in a cost-efficient, sensitive, and reproducible manner. In addition, funding for clinical trials of repurposed drugs may be difficult to acquire, which may lead clinicians and insurers to an uncertain position of whether to use certain treatments. However, with recent dramatic advances in remyelination research, we are optimistic that many new remyelination treatments for MS will arise and be in use in the next decade or so.

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REVIEW

Prevalence, clinical features and treatment of depression in Parkinson's disease: An update

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Abstract

Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases which typically affects individuals over 65 years. Although the symptomatology is predominantly motor, neuropsychiatric manifestations, *e.g.*, depression, apathy, anxiety, and cognitive impairment occur in the course of the illness and can have a great impact on the quality of life in these patients. Parkinson's disease is commonly comorbid with depression with prevalence rates of depression, generally higher than those reported in general population. Depression in PD is frequently underestimated and consequently undertreated, which have significant effects on the quality of life in these patients. The neurobiology of depression in PD is complex and involves alterations in dopaminergic, serotonergic, noradrenergic and possibly other neurotransmitter systems which are affected in the course of the disease. The tricyclic antidepressants and the selective serotonin reuptake inhibitors are the two classes of antidepressant drugs used for depressive symptoms in PD. Several published studies suggested that both classes are of comparable efficacy. Other serotonergic antidepressants, *e.g.*, nefazodone and trazodone have also been of benefit. Meanwhile, there are limited data available on other drugs but these suggest a benefit from the serotonin and noradrenaline reuptake inhibitors such as mirtazapine, venlafaxine, atomoxetine and duloxetine. Some of the drugs used in symptomatic treatment of PD, *e.g.*, the irreversible selective inhibitors of the enzyme monoamine oxidase-B, rasagiline and selegiline as well as the dopamine receptor agonist pramipexole are likely to have direct antidepressant activity independent of their motor improving action. This would make these drugs an attractive option in depressed subjects with PD. The aim of this review is to provide an updated data on the prevalence, clinical features of depression in subjects with PD. The effects of antiparkinsonian and antidepressant drugs on depressive symptoms in these patients are also discussed.

Key words: Antidepressant drugs; Depression; Serotonin reuptake inhibitors; Parkinson's disease; Tricyclic antidepressants

Core tip: The development of depressive symptoms in Parkinson's disease (PD) has important implications on the daily functioning and quality of life. It is thus important to diagnose and treat depression effectively in these patients. This review aims to discuss the

prevalence, associated factors and drugs used to treat depressive symptoms in PD.

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INTRODUCTION

Idiopathic Parkinson's disease (PD), also known as primary PD or paralysis agitans is the second most common neurodegenerative disease[1]. The disease affects about 1% of the population over the age of 65 years[1,2]. Estimates of the prevalence of PD in Europe vary from 65.6-12500 per 100000, while annual incidence estimates vary from 5-346 per 100000[3,4]. The disease is characterized by a triad of motor symptoms, bradykinesia, rigidity and resting tremors[5]. These symptoms result from the loss of dopaminergic neurons in the substantia nigra pars compacta, with consequent depletion of dopamine in the striatum[6,7]. Other neuronal populations are also affected including serotonergic, noradrenergic and cholinergic systems, which contributes to the development of non-motor symptoms during the course of the disease[8]. Neuropsychiatric symptoms such as depression, apathy, anxiety, sleep disturbances, cognitive impairment occur in the premotor or presymptomatic phase of the disease, as well as in the advanced disease, and can substantially affect the quality of life and activities of daily living[9-11]. The pathophysiology of these symptoms is complex, and reflects the widespread cortical and brainstem pathology and affection of several neurotransmitter pathways[12]. Depression is particularly common in PD patients, is frequently overlooked, and is known to cause significant morbidity[13]. In this paper it is aimed to provide a comprehensive and an updated account on the prevalence and clinical features of depression in subjects with PD. The effect of antiparkinsonian drugs on the course of depression in these patients as well as the tolerability and efficacy of antidepressant medications are presented. Non-pharmacological approaches to treat depression in patients with PD are also discussed.

DEPRESSION

Mood disorders can be subdivided into: (1) unipolar (depressive) disorders; (2) bipolar disorders (formerly manic-depressive illness); and (3) other mood disorders, *e.g.*, psychotic mood disorders, postpartum mood episodes with psychotic features, mood disorders due to a general medical condition, and substance/medication-induced mood disorder[14-16]. The term depression describes a range of mood disturbance in the form of an unhappy or sad mood to markedly decreased mood[16]. There are two diagnostic classifications for depressive disorders. One is the "International Classification of Disorders", 10th edition (ICD-10) system of the World Health Organization[14]. The other is the "Diagnostic and Statistical Manual of Mental Disorder", 5th edition (DSM-V) from the American psychiatric association[15]. The diagnosis of major depression illness depends on the presence of a number of symptoms that include depressed mood, loss of interest or pleasure, significant weight loss, or weight gain, sleep disturbances, psychomotor agitation or retardation, fatigue, loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, or indecisiveness, recurrent thoughts of death or suicidal ideation. One of the symptoms should be either depressed mood or loss of interest or pleasure in usual activities (DSM-V)[15] (Table 1). Symptoms must have been present almost every day for a minimum of 2 wk, represent a change from previous functioning, result in clinically significant distress or impairment in social, occupational, or other important areas of functioning, and are not due to a medication, substance abuse or a general medical condition.

Other types of depressive disorders include disruptive mood dysregulation disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder[15]. Depression might occur in the sitting of medical diseases, especially chronic illnesses such as diabetes mellitus, congestive heart failure, myocardial infarction, rheumatologic disorders. Depressive symptoms can be associated with other psychological diseases, including psychotic disorders[17] or caused by a number of medications including β-adrenoceptor blockers, α-adrenoceptor blockers, digoxin, calcium channel blockers, methyldopa, corticosteroids, psychostimulants , isotretinoin, and interferon-α[18-21]. Depressive symptoms are also a common and often characteristic feature in a number of neurological disorders such as stroke, PD, multiple sclerosis, or epilepsy, in which depression has a strong impact on both quality of life and outcome of the primary neurological disorder[22].

PREVALENCE AND FEATURES OF DEPRESSION IN PD

The estimated lifetime prevalence of depression in the general population is approximately 17%-20%[23,24]. It is estimated that up to 85% of patients will have more than one episode in their lifetimes[23,25]. Moreover, up to 20% of patients with depression will have symptoms lasting for 2 years or more, *i.e.*, chronic depression[23,25]. Prevalence estimates for depression

Table 1 Diagnostic criteria for major depressive episode

Depressed mood most of the day, nearly every day
Markedly diminished interest or pleasure in all or almost all activities
Significant weight loss when not dieting or weight gain
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt
Diminished ability to think or concentrate, or indecisiveness
Recurrent thoughts of death or suicidal ideation

Five or more of the symptoms must have been present during the same 2-wk period, represent a change from previous functioning and cause significant distress or impairment in social, occupational or other functioning. One of the symptoms should be either depressed mood or loss of interest or pleasure, significant weight loss or weight gain. Symptoms should be present nearly every day, most of the day are not due to drug or a general medical condition. Criteria adapted from Diagnostic Statistical Manual of Mental Disorders[15].

in PD vary in different studies, but are clearly higher than those reported in general population. Studies in general report a prevalence rate between 21% and 40%[26-32]. Prevalence rates as low as 2.5% and as high as 66% have also been reported[33-52] (Table 2). It has been found that persons treated with antiparkinson drugs had significantly increased rate of subsequent antidepressant drug treatment compared with controls, indicating the high frequency of depression in PD[53]. Moreover, initiation of any antidepressant drug therapy was associated with a higher risk of PD in the 2 years from the beginning of treatment. This suggested that depressive symptoms were an early manifestation of PD, before the appearance of motor symptoms[54]. Jasinska-Myga *et al*[36] found that 72% of patients developed depression within ten years of symptomatic PD onset (mean time to depression: 7.9 years). Becker *et al*[55] reported approximately twofold increased risk of developing depression in PD patients when compared to PD-free population.

Depression itself might be an independent risk factor for developing PD. This is because in patients with depression followed up for 10 years, 1.42% developed PD compared with 0.52% in the control group. In this study, patients with depression were 3.24 times more likely to develop PD compared with the those of the control group[56]. Moreover, patients with psychiatric illnesses exhibited 2.38-fold increased risk for developing PD compared with nonpsychiatric individuals. The highest risk for developing PD was observed in patients with schizophrenia[57]. The risk of the onset of major depression is influenced by genetic factors. This is due at least in part to the effect of genetic factors in modulating the individual's response to the depression-inducing effect of stressful life events[58]. Vanderheyden *et al*[37] found that 30% of PD patients had a history of mood disorder and 46% were prescribed an anxiolytic, an antidepressant, or an atypical neuroleptic, or a combination of these drugs. A study on first-degree relatives of patients with PD showed increased risk of depressive and anxiety disorders compared with first-degree relatives in the control group[59]. Puschmann *et al*[60] described a family with mild and slowly progressive L-dopa responsive autosomal dominant PD whose members also had depression. This suggests a common genetic vulnerability for mood disorders and PD.

The clinical manifestations of PD depression include apathy, psychomotor retardation, memory impairment, pessimism, irrationality, and suicidal ideation without suicidal behavior[61]. Depressed PD patients share many features that are present in depressed subjects without PD such as apathy, loss of initiative and decisiveness, insomnia, lack of energy and fatigue. The clinical spectrum of depression in PD patients differs in that features such as anhedonia, sadness, feelings of self-blame, feelings of guilt, sense of failure, self-destructive thoughts, suicide or suicidal ideation are much less common compared to patients with major depression not having PD. Concentration problems, however, are more common compared with depressed control subjects[62,63]. Suicidal ideation is not only a feature of major depression illness but also occurs in other neurological diseases, *e.g.*, multiple sclerosis, epilepsy, Huntington's disease, and PD. The most common risk factors being hopelessness, depression, and social isolation[64-66]. Major depression is a major risk factor for suicide and suicidal acts, which usually occur during major depressive episodes or mixed episodes[67]. Sokero *et al*[68] found that during the current major depressive episode, 58% of all patients had experienced suicidal ideation and 15% had attempted suicide most of whom (95%) had also had suicidal ideation. The severity of depression and current alcohol dependence or abuse was among factors that predicted suicide attempts. In their study, Subramaniam *et al*[69], reported that the prevalence of suicidal ideation, plan, and attempt to commit suicide among patients with lifetime major depressive illness was 43.6%, 13.7% and 12.3%, respectively. Inagaki *et al*[70] reported current suicidal ideation in 71.4% of patients with major depressive illness.

Suicide or death ideation are also common in depressed patients with PD. Kostić *et al*[71] found that in PD patients, followed for 8 years, the suicide-specific mortality was 5.3 times higher than expected. Current death and/or suicidal ideation were present in 22.7% of the patients. Major depression, psychosis, and hopelessness were associated with such ideation. Nazem *et al*[72] found that death ideation or suicide ideation were present in one-third of the sample, and 4% had a lifetime suicide attempt; increasing severity of depression, impulse control disorder, and psychosis were associated with either ideation. A lifetime prevalence of suicidal ideation in 11.6% of PD patients was also reported; the presence of depression and history of impulse-control disorder behaviors were important risk factors[73]. Other workers reported a prevalence of suicidal ideation in 14.4% of their sample but no attempted suicide; major depression being the

Table 2 Classification, mechanism of action and dosage range of antidepressants

Class	Mechanism of action	Generic name (trade name)	Dose range (mg/d)
Older antidepressants			
Mixed serotonin and norepinephrine reuptake inhibitors			
First-generation tricyclic antidepressants	Inhibit neuronal reuptake of norepinephrine and serotonin	Amitriptyline (elavil)	100-300
		Clomipramine (anafranil)	100-250
		Doxepin (adapin)	100-300
		Imipramine (tofranil)	50-300
		Trimipramine (surmontil)	100-300
		Protriptyline (vivactil)	75-200
		Lofepramine	15-60
Second-generation tricyclic antidepressants	Inhibit neuronal reuptake of norepinephrine and serotonin	Desipramine (norpramin)	100-300
		Nortriptyline (pamelor)	50-150
Tetracyclic antidepressants	Inhibit neuronal reuptake of norepinephrine and serotonin	Maprotiline (ludiomil)	100-200
		Amoxapine (asendin)	50-300
Heterocyclic agents Triazolopyridines	Mixed serotonin effects: Serotonin (5-HT2A) receptor blockade with serotonin reuptake inhibition	Trazodone (desyrel)	150-400
Monoamine oxidase inhibitors	Nonselective inhibitor of monoamine oxidase A and B	Phenelzine (nardil)	60-90
		Tranylcypromine (parnate)	20-60
		Selegiline (eldepryl)	5-10
Newer antidepressants			
Selective serotonin reuptake inhibitors	Selectively inhibit the reuptake of 5HT at the presynaptic neuronal membrane. Sertraline also markedly inhibits dopamine reuptake	Fluoxetine (prozac)	20-60
		Fluvoxamine (luvox)	100-300
		Paroxetine (paxil)	20-50
		Sertraline (zoloft)	50-200
		Citalopram (celexa)	20-40
		Escitalopram (lexapro)	5-20
Serotonin and noradrenaline reuptake Inhibitors	Potent inhibitors of 5HT and norepinephrine uptake; weak inhibitors of dopamine reuptake	Venlafaxine (effexor)	75-350
		Milnacipran (savella)	12.5-100
		Duloxetine (cymbalta)	60
Norepinephrine reuptake inhibitors	Noradrenaline reuptake inhibitor. Inhibits norepinephrine reuptake without inhibiting serotonin reuptake	Viloxazine	150-300
		Reboxetine (edronax)	4-8
		Atomoxetine (strattera)	40-80
Reversible inhibitors of monoamine oxidase A	Selective, reversible inhibitors of monoamine oxidase A: resulting in increased concentrations of NE, 5-HT, and dopamine in synapse	Moclobemide	300-600
		Brofaromine	75-150
5HT2 receptor antagonists/reuptake inhibitor serotonin modulators	Mixed serotonin effects. Inhibition of the reuptake of serotonin and selective postsynaptic 5-HT2A blockade	Nefazodone (serzone)	300-600
		Desvenlafaxine (pristiq)	50 mg once daily
		Ritanserin	5-10
5HT1a receptor agonists	Partial agonist of serotonin 5-HT1a	Gepirone, ipsapirone, tandospirone, felsinoxan	
α2-noradrenergic antagonists	Complex action on serotonin and noradrenaline *via* Serotonin (5-HT2A and 2C) receptor blockade and presynaptic α2-receptor blockade	Mirtazapine (remeron)	15-45
GABA-mimetics	GABAA and GABAB receptor agonists	Fengabine	900-1800
Dopamine reuptake inhibitors	Increases activity of norepinephrine and dopamine only; no significant effect on serotonin	Buproprion (wellbutrin)	200-450
Melatonin receptor agonists	Melatonin MT1 and MT2 receptor agonist and serotonin 5HT2C receptor antagonist	Agomelatine (valdoxan)	25-50
Herbal remedy: *Hypericum perforatum*/ St. John's wort	Unclear: inhibits the reuptake of several neurotransmitters, including 5HT, NE, dopamine, and γ-aminobutyric acid	*Hypericum perforatum*	300-900

Clomipramine, nefazodone and venlafaxine are potent non-selective serotonin reuptake inhibitors. Citalopram S-enantiomer, escitalopram, is the most active isomer and is a more potent and more selective serotonin reuptake inhibitor than citalopram. Extracts of *Hypericum perforatum* (St. John's Wort) are used in many countries to treat depressive disorders. GABA: Gamma aminobutyric acid; NE: Norepinephrine; 5HT: 5-hydroxytryptamine.

main predictor of suicidal ideation. Other factors were lower age of disease onset, panic disorder, and social anxiety disorder[74]. Interestingly, these figures are not higher than those reported in non-parkinsonian patients with major depression. It is noteworthy to mention that active suicidal ideation, lifetime suicidal attempts are associated with early-onset depression and young age[75]. The lower prevalence of suicidal ideation in depressed PD patients might be due to the fact that the disease occurs in old age.

FACTORS ASSOCIATED WITH DEPRESSION

Factors associated with depression include increased severity of motor disability, greater impairment in

activities of daily living[28,34,36,39,43,76], and longer disease durations[25,33,31,39,42,61]. Depression is more frequent in the young onset PD[34,43,45,76-78]. Similarly, those with subthreshold depression are younger (approximately 5 years) than non-depressed patients[27]. In contrast, Riedel *et al*[39] found that depression rates were already substantially elevated at early PD stages and that depression was not linked with age, age at onset of PD, or disease duration. In their study, van der Hoek[42] observed no difference in the prevalence of depression among the motor subtypes of PD. The authors, however, noted a trend towards higher prevalence of depression in the tremor dominant group of patients. In contrast, Dewey *et al*[79] found that patients with right-sided onset of tremor had a lower risk of depressive symptoms compared with other presentations. Meanwhile, the side and type of initial motor symptoms were not related to the risk of later cognitive impairment.

Gender imbalance is common in depression in non-PD subjects. McKercher *et al*[80] reported a prevalence of major depression of 5.5% for men and 11.6% for women. The prevalence of atypical depression is also higher in women than in men (24.6% *vs* 17.3%)[81]. Studies also suggested that depressive symptoms were more likely to occur in females than in males[42,82,83]. Other researchers observed no significant difference in the prevalence of depression between men and women with PD[42].

Stressful life events have been implicated in the onset of episodes of major depression[58]. Stressful life events are independent predictors of depressive symptoms in older adults[84] and in those who experience depression recurrence, exposure to acute life events predicts the evolution of residual symptoms to recurrence[85]. Depression in PD is associated with a history of anxiety disorder and memory problems[34] and with dementia[39]. Having a history of depression prior to onset of PD was predictive of depression with PD[45]. Significantly more serious depression also occurs in subjects with a history of depression before PD compared with those without such history[86]. Rod *et al*[46] suggested an important role for life events in onset of depression in patients with PD. The authors found that more than 50% of their sample experienced major life events since diagnosed with PD with major depression occurring in 9.9%. It was also noted that each additional event was associated with a 56% higher risk of depression. These observations stress the importance of social support in the management of PD patients with depression. Stressful life events are also important in non-PD depressed subjects.

Anxiety, memory problems, hallucinations, sleep disturbances are more common in depressed PD patients compared with PD patients without depression[34,76]. Apathy, a possible feature of depression, can exist independently and is often associated with cognitive impairment[87]. Depression in PD is often associated with anxiety[28,34,41,50] and both depression and anxiety might be early symptoms during the prodromal phase of PD[88]. Anxiety and apathy are significant comorbid conditions of moderate and severe depression[89]. Anxiety coexisted with depression in 8.6%[66] or 41% of the PD patients[50]. The figures are not higher than those encountered in non-PD patients. Thus, in patients with current episode of depression, generalized anxiety disorder and panic disorder comorbidities were associated with unipolar depression in 37.1% and 31.4% of patients, respectively[90]. In late-life depression in non-PD subjects, the prevalence rate of comorbid anxiety disorders was 38.6%[91]. Brown *et al*[44] suggested the presence of two clinical phenotypes of depression in depressed PD subjects, "anxious-depressed" and "depressed", with a large proportion of patients have relatively isolated anxiety. Depression and anxiety disorders were often unrecognized and untreated and the comorbidity greatly exacerbated PD symptoms[92]. It is likely that anxiety and depression in PD are due to different pathophysiological mechanisms[41].

COURSE OF DEPRESSION AND THE EFFECT OF DOPAMINERGIC DRUGS

Symptoms of depression are among the most frequent non-motor symptoms in the premotor phase of the disease. de la Riva *et al*[9] reported that newly diagnosed, untreated patients with PD experienced more depression, fatigue, apathy, and anxiety than healthy controls all time points; these remained relatively stable in early disease. Depression and other neuropsychiatric symptoms appear to be amenable to antiparkinsonian drug therapy, suggesting that they are related to or part of the disease process. In this context, Nègre-Pagès *et al*[41] found that patients with depressive symptoms received more frequently levodopa and less frequently a dopamine agonist. Similar observations were reported by Hanganu *et al*[93] who found that higher levodopa (L-dopa) dosages correlated with worse depressive symptoms. In contrast, there was no significant correlation between dopamine agonists and worsening of depressive symptoms. Spalletta *et al*[10] found significant improvement over time in the depression severity (also memory performance, and motor symptoms) in newly diagnosed patients with PD after 6-12 mo of antiparkinsonian therapy. Kulisevsky *et al*[94] found that among neuropsychiatric symptoms in PD, only depression was influenced by the type of medication, being less prevalent following treatment with dopaminergic receptor agonists. This suggested that depression in these patients is related to the dopaminergic deficit. Other neuropsychiatric symptoms such as impulse control disorders and excessive daytime sleepiness, however, are increasingly associated with the use of these drugs[9]. Even *et al*[95] identified three possible subtypes of comorbid depression associated with PD. The first category of patients is those who would develop depression even if they had no PD

(nonspecific-casual comorbid dPD). The second subtype includes patients who would be depressed because of another disabling medical illness (nonspecific-reactive comorbid dPD). The third group of patients are those in whom depression is directly related to the underlying pathophysiology of PD (specific comorbid dPD). This latter subtype might be partly responsive to dopamine replacement, suggesting a role for other neurotransmitter systems in its pathogenesis. There are data, however, that suggest a negative impact of dopaminergic pharmacotherapy on cognitive function in depressed PD patients in contrast to non-depressed patients who performed better while on dopaminergic medication[96].

Some dopaminergic medications appear to have antidepressant action unrelated to their influences on motor function. Pramipexole is a non-ergot dopamine receptor agonist which has been shown to be effective in reducing unified Parkinson's Disease Rating Scale (UPDRS) in early PD and as an "add on" therapy in advanced disease[97,98]. The UPDRS is used to assess both motor and nonmotor symptoms by listing numerous items to be scored by the examiner[5]. Studies suggest that pramipexole possesses a direct antidepressant effect. Thus, Barone *et al*[99] compared pramipexole to sertraline in a randomized trial in PD patients with major depression but no motor complications. They found that both agents decreased depression scores throughout treatment. The proportion of patients who recovered was significantly higher in the pramipexole compared to the sertraline group (60.6% *vs* 27.3%). In an open study of pramipexole as an add-on to L-dopa therapy or single administration, the scores of depressive symptoms, UPDR Scale III, and freezing of gait improved. No correlation was observed between depression scores and motor functions, suggesting an antidepressant effect for pramipexole[100]. Barone *et al*[101] conducted a 14-wk randomized trial comparing pramipexole with placebo in patients with mild-to-moderate PD without motor fluctuations who had depressive symptoms. The authors found that pramipexole improved depressive symptoms. Selegiline and rasagiline are irreversible selective inhibitors of the enzyme MAO-B that are effective as an initial monotherapy in early PD and as adjunct therapy to L-dopa in advanced PD[102-104]. Frampton *et al*[105] tested the efficacy of selegiline transdermal application in a randomized, double-blind, multicentre studies in adult outpatients with major depressive disorder. They found that short-term treatment with selegiline (6-12 mg/d) was superior to placebo on most measures of antidepressant activity. Long-term treatment with a fixed dose of 6 mg/d selegiline was also superior to placebo as maintenance therapy. In addition to improving motor performance, treatment with rasagiline (2 mg/d) in newly diagnosed PD patients who also have comorbid untreated depression, has been shown to improve depression symptoms. Rasagiline appears to have direct antidepressant action since it especially improved symptoms uninfluenced by motor function such as mood, guilt, psychic anxiety, and hypochondria[106].

NEURO-IMAGING STUDIES

It has been suggested that the development of depression in PD is likely to represent an advanced and widespread neurodegeneration of both serotonergic and dopaminergic neurons[76]. Imaging studies suggested that brain dopamine deficiency might have a role in depression in PD patients. Studies with 18F-fluorodopa-PET in *de novo* unmedicated PD patients showed that higher depression scores were associated with lower striatal 18F-fluorodopa uptake, suggesting that impaired striatal dopaminergic function is related to depressive symptoms in these subjects[107]. Other studies using [(123) I] FP-CIT single photon emission computed tomography (SPECT) tracer binding to the dopamine transporter (DAT) reported significant decrease in DAT availability in patients with PD. There was an association between dopamine loss in the caudate nucleus (lower DAT binding) and depressive symptoms[108,109]. In one study, reduced DAT binding was reported in the striatum in the majority of patients with major depression, indicating a role for dopamine hypofunction in this disorder. A more pronounced decrease in DAT binding occurred in PD patients (SPECT imaging using 99mTc-TRODAT-1)[110]. Bui *et al*[111] suggested that the decrease in striatal uptake in the context of a depressive episode might be reversible. The authors observed improved PD symptoms and increased DAT uptake {[(123) I] FP-CIT SPECT} in a depressed PD patient following treatment with electroconvulsive therapy. Ceravolo *et al*[112], however, reported increased bilateral striatal (123) I-FP-CIT uptake (DAT density) associated with the severity of both depressive and anxious symptoms in newly diagnosed PD patients. This was attributed to a lack of compensatory mechanisms and that it might have a pathogenic role in affective symptoms by reducing the dopaminergic tone in the synaptic cleft.

Not only dopaminergic pathways are affected in PD, but also cholinergic, serotonergic, and noradrenergic ones[113,114]. The neurobiology of depressive disorders involves alterations in serotonergic, dopaminergic and noradrenergic neurotransmission[115,116]. This forms the basis for the use of drugs such as tricyclic antidepressants (TCAs), serotonin reuptake inhibitors, noradrenaline reuptake inhibitors in the pharmacological management of depressive disorders[117,118]. Politis *et al*[119] used ^{11}C-DASB PET, a selective *in vivo* marker of 5-HT transporter binding to assess serotonergic function in patients with PD. They found relatively higher ^{11}C-DASB binding in raphe nuclei and limbic structures in those with highest scores for depression symptoms which might reflect reduced extracellular serotonin levels and decreased serotonergic neurotransmission. Beucke *et al*[120] suggested that un-medicated PD

patients have a low serotonergic activity which might be related to the dopamine deficit. Thus, auditory evoked potentials (indicator of central serotonergic function) were decreased in patients with PD compared with healthy subjects, but this difference was abolished following L-dopa treatment for 12 wk. The authors also noted a trend towards a correlation between auditory evoked potentials and DAT of the unmedicated patients [using (123) I-FP-CIT SPECT].

NEED FOR ANTIDEPRESSANT DRUG THERAPY

The presence of depression in PD subjects is under-recognized and consequently untreated. For instance, Althaus *et al*[121] reported a prevalence of depressive symptoms in 35.4% of their sample. Antidepressant drugs, however, were prescribed in 25.0% of patients suffering from moderate to severe depression. Moreover, depression was largely undertreated because a significant proportion of patients continued to experience depressive symptoms despite antidepressant drug therapy. In another study minor and major depression were found in 36.3% and 12.9% of the subjects, respectively. Only 8.6% of the minor depressed patients and 30.3% of the major depressed patients were prescribed antidepressant drugs[42]. Moreover, de la Riva *et al*[9] found that approximately two-thirds of patients with PD who screened positive for depression were not taking an antidepressant.

The development of depression in subjects with PD has a major impact on the quality of life and activities of daily living. The presence of neuropsychiatric symptoms such as depression, apathy, sleep disturbance and anxiety is associated with more severe parkinsonism compared with patients without these symptoms[29]. Depression also impacts on other cognitive functions. In one study, significant subjective memory complaints were reported by approximately 15% of PD patients and these worsen with increasing severity of depressive symptoms[32]. Subjects with left hemibody onset of motor symptoms and depression exhibited worse working memory, greater disability and lower quality of life compared with those without depression (and also relative to depressed subjects with left hemibody onset of motor symptoms)[122]. It has also been suggested that the presence of depressive symptoms (as well as dopaminergic drugs, disease severity and the occurrence of cognitive impairment) might underlie the onset of psychotic type symptoms in the early stages of PD[123]. Successful treatment of depression leads to important, sustained improvements in the quality of life and disability in PD patients[124].

ANTIDEPRESSANT DRUGS

The TCAs and the monoamine oxidase inhibitors (MAOIs) were the first classes of drugs employed in the pharmacological management of depressive symptoms. These agents work by increasing the synaptic concentration of the monoamine neurotransmitters; norepinephrine (NE), serotonin [(5-hydroxytryptamine, (5HT)] and dopamine. The MAOIs inhibit the enzymatic metabolism of neurotransmitters. The TCAs inhibit the neuronal uptake of NE and 5HT. The TCAs dominated the pharmacological management of depressive disorders for more than 30 years. With the advent of the new generations of antidepressants such as the selective serotonin reuptake inhibitors (SSRIs), the serotonin and noradrenaline reuptake inhibitors (SNRIs) and the noradrenaline reuptake inhibitors (NRIs), TCAs are no longer considered first-line treatments[125-127]. Table 2 lists different classes of antidepressant drugs and their mechanism of action.

ANTIDEPRESSANTS USED IN PD

TCAs

These include the tertiary-amine tricyclics, such as clomipramine, imipramine, amitriptyline, doxepin and trimipramine, and the secondary amines, such as desipramine, protriptyline and nortriptyline. These drugs owe their antidepressant properties to inhibition of the neuronal uptake of the monoamine neurotransmitters; norepinephrine, and serotonin (5-hydroxytryptamine, 5HT). Individual agents differ in their relative potency to inhibit the reuptake of either NE or 5HT. The tertiary tricyclics, amitriptyline, imipramine, and clomipramine are more potent in blocking the serotonin transporter while the secondary tricyclics are much more potent in blocking the norepinephrine transporter. These drugs as well as the tetracyclic compounds maprotiline and amoxapine have been approved for use in major depression with the exception of clomipramine, which in the United States is approved for use only in obsessive-compulsive disorder[128,129]. The TCAs dominated the pharmacological management of depressive disorders for more than 30 years. With the advent of the new generations of antidepressants such as the SSRIs, SNRIs and the NRIs, TCAs are no longer considered first-line treatments[125-127]. The TCAs have the capacity to block alpha1-adrenergic, H1 histaminergic and muscarinic receptors. The side effects include anticholinergic effects such as dry mouth, blurred vision, urinary retention and constipation. Sedative and cognitive effects should make their use in the elderly be largely avoided. Their slowed clearance in old age leads to drug accumulation and increased frequency and severity of side effects[13,130]. TCAs also cause weight gain, and sexual dysfunction[131]. TCAs cause cardiac conduction defects and arrhythmias by blocking fast inward Na^+ channels on myocardial cells. Blockade of postsynaptic peripheral α-adrenergic receptors contributes to the postural hypotension associated with TCA use[132]. The use of antidepressants in general and in particular TCAs is associated with tachycardia[133].

TRICYCLIC ANTIDEPRESSANT DRUGS IN PARKINSON'S DISEASE

TCAs were the first class of antidepressant medications to be used for the treatment of depression in patients with PD. These agents were found more effective than placebo and even better than some of the SSRIs. Thus, Andersen *et al*[134] treated patients with nortriptyline for 16 wk and observed larger improvement compared with placebo. A meta-analysis by Frisina *et al*[135] of 24 placebo-controlled trials found that TCAs had a greater antidepressant effect relative to SSRIs and the mono-amine-oxidase inhibitor, selegiline. Side effect profile was, however, in favor of SSRIs. A more recent meta-analysis by Liu *et al*[136] concluded that TCAs might be the best choice when starting antidepressant treatment in patients of PD. In a study comparing amitriptyline and fluoxetine, Serrano-Dueñas[137] found that amitriptyline (approximately 35 mg/d) was better than fluoxetine at controlling the depression. Side effects that occurred in 15% of the patients on amitriptyline treatment, however, led these patients to abandon the drug. Antonini *et al*[138] compared low-dose amitriptyline (25 mg) to the SSRI sertraline (50 mg) on depression and quality of life in a prospective single-blind randomized study. Drugs were administered for 3 mo. Responder and completion rates were 83.3% and 75% for sertraline and 72.7% and 73% for amitriptyline, respectively. Sertraline and not amitriptyline treatment had a significant benefit on quality of life. (Whether the dopamine reuptake inhibition by sertraline is involved is an intriguing possibility!).

The short-term efficacy of desipramine was compared to that of citalopram, a SSRI in a double-blind, randomized, placebo-controlled study. The authors found that desipramine induced a more rapid improvement (after 14 d) in depression score than did an SSRI and placebo. After 30 d both drugs significantly improved depression. Thus a predominantly noradrenergic reuptake inhibitor TCA was faster than an SSRI in controlling depression in PD[139]. Moreover, nortriptyline, another TCA which mainly inhibits noradrenaline reuptake was found superior to placebo in decreasing depression scores. In this randomized, placebo controlled trial, the SSRI paroxetine controlled release (CR), however, was not efficacious. Response rates for nortriptyline, paroxetine CR, and placebo were 53%, 11%, and 24%, respectively[140].

TCAs possess antihistaminic effects which might be of benefit in those suffering from insomnia. One randomized pilot study assessed non-pharmacologic treatment or doxepin, compared to placebo in PD patients with insomnia. Compared to placebo, doxepin improved insomnia, sleep quality, clinical global impression of change. The drug also reduced fatigue severity and improved cognitive scores[141]. Clomipramine, a drug with prominent 5HT reuptake inhibitory action was reported to improve delusions and hallucinations in a parkinsonian patient with psychosis and comorbid depression[142].

Recently, a study by Paumier *et al*[143] in early PD patients showed that TCAs resulted in delaying the time to initiation of dopaminergic therapy compared with patients not on antidepressants. There were no changes in Unified PD Rating Scale (UPDRS) scores. The effect of TCAs thus could not be attributed to symptomatic effects.

Table 3 lists selected studies on the effect of TCAs on depressive symptoms in subjects with PD.

SSRIs

These agents are considered first line treatments of depression due to their more safety profile compared to the TCAs[144]. The SSRIs differ in their potency and selectivity in inhibiting serotonin reuptake and in their pharmacokinetics. The prototype SSRIs is fluoxetine which acts by blocking the reuptake of 5HT at the presynaptic neuronal membrane, thereby increasing its concentration in the synaptic cleft[145]. Fluoxetine has longer elimination half-life of 1-3 d after acute administration, while its active metabolite norfluoxetine has a half life of 7-15 d[128]. Its abrupt cessation is not likely to cause discontinuation reactions[146].

Fluvoxamine and paroxetine are other potent SSRIs with an elimination half-life of 15 and 21 h, respectively[144,147]. The abrupt discontinuation of paroxetine results in withdrawal symptoms, including nightmares, tremor, dizziness, insomnia, myalgias, and a "flu-like" syndrome[148]. It is thus advisable to taper the medication over several days, particularly in patients receiving more than 20 mg per day[145]. The drug is a first-line treatment option for major depressive disorder, dysthymia or minor depression[149].

The inability of citalopram to cause significant inhibition of hepatic enzymes made the agent an attractive agent for the treatment of depression, especially among the elderly and patients with comorbid illness requiring concomitant medicines[150,151]. Escitalopram is the pure S-enantiomer of the racemic compound citalopram and the pharmacologically active enantiomer of the racemate which have a more potent antidepressant than that of citalopram. Escitalopram is approximately 30-fold more potent than R-citalopram[152,153].

The SSRIs affect the reuptake of other neurotr-ansmitters. Thus, fluoxetine also acutely increases the extracellular concentrations of NE and dopamine (as well as 5HT) in prefrontal cortex[154] and unlike the other SSRIs possesses moderate affinity for the serotonin 2C receptor[152]. Paroxetine and sertraline possess moderate affinity for the human NE transporter and dopamine transporter, respectively[152]. Sertraline has been shown to increase extracellular levels of dopamine in the nucleus accumbens and striatum[155] which might have important clinical consequences. Paroxetine displays affinity for the muscarinic cholinergic receptor and causes a higher rate of anticholinergic effects, such as dry mouth, constipation, and cognitive

Table 3 Prevalence of depressive symptoms in subjects with Parkinson's disease in different studies

Stage of PD/type of patients	No. of patients/ sample size	Prevalence of depression/ depressive symptoms	Prevalence of other neuropsychatric symptoms	Ref.
Outpatients, non-fluctuating (21 de novo, 69 treated with levodopa or dopamine agonists)	90	Major depression in 21.1% (*vs* in 3.3% controls)	Panic disorders in 30% (*vs* 5.5% in controls) Dystimia in 18.8% (*vs* 4.4% in controls)	[26]
Outpatients with established PD	100	Major depression in 35%		[35]
Patients with PD presenting with non-motor symptoms. Retrospective study of pathologically-proven PD	91	Depression in 2.5%	Anxiety in 3.9%	[33]
Outpatients with established PD	50	Major depression in 42% (*vs* 10% of geriatric patients)		[28]
Nondemented patients with moderate to severe PD	111	Depression in 26.1% Subthreshold depression in 28.8%		[27]
Early untreated PD	175	Depression in 37%	Apathy in 27% Sleep disturbance in 18% Anxiety in 17%	[29]
New-onset PD patients	685	Depression in 72% (developed depression within ten years of symptomatic PD onset)		[36]
Outpatients with established PD	1086	Major depression in 15.6%		[37]
Outpatients with established PD	1449	Depression in 25%	Anxiety in 20% Dementia in 29% Psychotic syndromes in 12.7% Sleep disturbances in 49%	[38]
Outpatients with established PD	1449	Depression in 33.6%		[39]
Outpatients with established PD	150	Depression in 43% Depression without apathy in 13%	Apathy only in in 17% Apathy + depression in 43%	[40]
Non-demented PD subjects	105	38% borderline depression Major depression in 4.8%		[30]
Non-demented PD subjects	450	Depressive symptoms in 40% (*vs* 10% of controls)	Probable anxious signs in 51% (*vs* 29% of controls)	[41]
Patients with established PD	256	Minor depression in 36.3% Major depression in 12.9%		[42]
Patients with established PD	360	Depression in 41.3%	Only apathy in 23% Apathy + depression in 36.9%	[43]
Patients with established PD	202	Depression in 37.3%	Anxiety in 31.3%, Dementia in 25.3% Excessive daytime sleepiness in 59.4%	[31]
Patients with established PD	513	Depression in 8.6%	Anxiety alone in 22.0% Anxiety + depressive symptoms in 8.6%	[44]
Outpatients with established PD	158	Depression in 11% to 57% (depending on the definition of depression)		[45]
Outpatients with established PD	639	Depression in 66%		[34]
New-onset PD patients	221	Major depression in 9.9% (developed depression over 3-4 yr)		[46]
Outpatients with established PD	1449	Depression in 18.8%	Dementia in 13.9% had Dementia + depression in 14.3%	[47]
Non-demented PD subjects	95	Depression in 28%		[48]
Early stage PD	36	Depression in 36.1%	Anxiety in 27% Obsessive-compulsive symptoms in 52.8% Somatization in 66.7%	[49]
Outpatients with established PD	117	Depression in 56%	Anxiety in 55%	[50]
Patients with established PD (ambulatory and home residents)	886	Depression in 24.4%	28.4% dementia (20.6 % of ambulatory and 85.7 % of home residents)	[51]
PD patients with mild cognitive impairment	104	Depression in 40.4% (*vs* 16.6% in controls)	Subjective memory complaints 16.3% (*vs* 7.7% of controls)	[32]
Non-demented PD subjects	115	Major depression in 28.7% Subthreshold depression in 26.10%		[52]

PD: Parkinson's disease.

disruption, compared with other SSRIs. These effects may be particularly difficult to tolerate for elderly or concomitantly medically ill patients[156]. There are also data to suggest that long-term treatment with paroxetine increases GABA, glutamate, dopamine and noradrenaline levels in the brain[157].

The most common side effects associated with SSRIs include initial nervousness or agitation, anxiety, headache, insomnia, dizziness, dry mouth, gastrointestinal symptoms (nausea, diarrhea, constipation) and sexual dysfunction[144,158]. The use of SSRIs is likely to increase the risk of upper GI bleeding, and this effect is potentiated when these drugs are used in combination with nonsteroidal anti-inflammatory drugs or low-dose aspirin. Other antidepressant drugs did not appear to have an effect on the risk of upper GI bleeding[159]. Other studies reported increased risk of upper gastrointestinal bleeding after short-term SSRI use (7-28 d) intake in male but not female patients[160]. Prior use of SSRIs has also been implicated in increased stroke severity and mortality in patients with hemorrhagic stroke. This, however, was not seen in in SSRI users with ischemic stroke[161]. SSRI/SNRI antidepressants and in particular sertraline and escitalopram have been shown to increase the risk of hyponatraemia, especially in depressed patients aged > 63 years[162]. Recent evidence also implicates SSRIs with decreased bone mineral density and increased risk of hip fracture which appear to decline after discontinuation of these agents[163,164]. SSRIs are associated with a modest but statistically significant increase in the QTc interval with citalopram being associated with more QTc prolongation than most other SSRIs. The increase in QTc by TCAs is however, significantly greater than that of SSRIs[165].

SSRIs in PD

Case reports have associated some of the SSRIs with extrapyramidal side effects. Leo[166] in a review of case reports and case series of movement disorders attributed to SSRIs found that among the 71 cases reported in the literature, the most common side effect was akathisia, dystonia, parkinsonism, and tardive dyskinesia-like states, with a frequency of 45.1%, 292.%, 14.1% and 11.3% respectively. Fluoxetine was implicated in 74.6% of cases of SSRI-induced extrapyramidal symptoms. Other concomitant drugs that can contribute to the development of extrapyramidal symptoms were likely in 57.7% of reports. Caley *et al*[167] in a retrospective study of medical records of 23 outpatients with Parkinson's disease who were receiving or had received fluoxetine up to 40 mg/d, found that 20/23 of patients experienced no worsening of their symptoms.

Studies in PD patients with depression, however, have shown treatment with SSRIs to be mostly safe and efficacious. A study of 66 patients with non-fluctuating, depressed patients with PD found a significant improvement in depressive symptoms with citalopram, fluoxetine, fluvoxamine, and sertraline 6 months after starting treatment. There was no significant change in UPDRS scores. The study, however, comprised a small number of patients (15-16) in each drug subgroup[168]. Rampello *et al*[169] treated depressed (n = 16) and nondepressed (n = 14) PD patients with citalopram (up to 20 mg/d) and observed improved depressive symptoms in 15/16 patients with depression. Moreover, citalopram did not worsen motor performance and on the contrary improved bradykinesia and finger taps in subjects with and without depression on levodopa.

Studies have also indicated an ability of paroxetine to improve depression in depressed PD patients. Tesei *et al*[170] administered paroxetine (10-20 mg/d) to 65 outpatients with PD and depression and found improved depression scores in 52 patients after approximately 3 mo. Adverse reactions which occurred in 13 patients led them to stop treatment. There were also increased "off" time and tremor in 2 patients that reversed after stopping paroxetine. In another study by Ceravolo *et al*[171] 6 mo therapy of paroxetine (20 mg/d) improved depression without an effect on motor function (UPDRS scores). Reversible worsening of tremor was observed in one patient. Chung *et al*[172] who examined the motor effects of 2 wk of paroxetine and placebo on responses to 2-h levodopa infusions, found no effect for the drug on tapping scores or dyskinesia. Paroxetine increased baseline walking speed (prior to infusion) but with increased subjective perception of worsened balance. In a randomized, double-blind, placebo-controlled trial, both paroxetine and venlafaxine XR were efficacious in improving depression without effects on motor function. The mean 12-wk reductions in depression score were 6.2 points for paroxetine group and 4.2 points for venlafaxine XR[173]. A randomized, controlled trial of paroxetine CR, nortriptyline, and placebo in 52 patients with PD and depression, however, failed to demonstrate a benefit from paroxetine[142].

In their study, Kostić *et al*[174] administered fluoxetine at daily dose of 20 mg to patients with PD and mild depression. The authors reported significant improvement in depression and UPDRS scores. These correlated with steady state plasma concentrations of fluoxetine and its metabolite norfluoxetine. In an open label trial of 10 patients with PD and major depression, citalopram improved depression, anxiety and functional impairment significantly[175]. In another open-label study of 14 PD patients with major depression, escitalopram treatment was well tolerated with a significant decrease in depressive symptoms, although response rate was only 21%[176]. In a double-blind, randomized, placebo-controlled study of PD patients with major depression, citalopram (and desipramine) produced significant improvements in the depression score after 30 d[139].

Sertraline was found effective in relieving depression in patients with PD without significant effect on motor performance[177]. Sertraline was of comparable efficacy to amitriptyline in decreasing depression scores in PD patients with depression. In this prospective single-blind randomized study, the responder rates were 83.3% and 72.7% for sertraline and amitriptyline, respectively. Sertraline but not amitriptyline, improved quality of life (mobility, activities of daily living)[138]. Kulisevsky *et al*[178] in a large sample of 374 depressed PD patients of whom 310 completed the study found that treatment with sertraline decreased depressive scores and also improved UPDRS scores. There was

worsening of tremor in some patients. Sertraline in both the usual formulation and in the liquid oral concentrate was found efficacious in deceasing depressive scores. Quality of life improved with sertraline (clinical global impression-severity of illness scale and clinical global impression-global improvement scale scores) after 6 mo of treatment. This occurred without change in UPPDR Scale motor scores[179].

OTHER ANTIDEPRESSANTS

Trazodone and nefazodone

Trazodone and nefazodone are chemically related with complex serotonergic actions. These drugs antagonize 5HT2A and 2C postsynaptic receptors. Blockade of these receptors leads to facilitated neurotransmission through $5HT_{1A}$ receptors, which reduces anxiety levels. In addition both drugs inhibit the reuptake of 5HT to some extent. They thus possess antidepressant, and also some anxiolytic and hypnotic activity, and have favorable sleep architecture profile[180]. Nefazodone has weak affinity for cholinergic and noradrenaline α_1- adrenergic receptors and, therefore, is associated with less sedation and orthostatic hypotension than trazodone. The drug has favorable effect on sleep pattern in contrast to fluoxetine which has been shown to not improve sleep in depressed patients[181,182]. Thus, nefazodone would be suitable for depressed patients with prominent features of anxiety and agitation and loss of sleep[105]. Sedation, dry mouth, nausea, and dizziness are the more common adverse effects of nefazodone[183]. In the treatment of major depression, these agents do not differ from the SSRIs with respect to overall efficacy and tolerability[184].

In PD patients with depression, Avila *et al*[185] provided data suggestive of motor improvement (UPDRS score) after nefazodone, but not after fluoxetine treatment. Meanwhile, both drugs were equally effective as antidepressants. In another study, by Werneck *et al*[186] trazodone improved depression and motor function improved in the depressed patients treated with the drug.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant. The drug increases noradrenergic and 5HT transmission *via* presynaptic α_2-antagonism. Mirtazapine increases the release of NE from central noradrenergic neurons by blocking the presynaptic inhibitory α_2-autoreceptors. It blocks the inhibitory α_2 heteroreceptors on serotonergic neurons, resulting in increased release of serotonin. Mirtazapine also blocks histamine H1 receptors, thus causing sedation, but has little effect on acetylcholine, dopamine or noradrenaline α_1 receptors. The most common side effects are dry mouth, sedation, increased appetite, and weight gain[144,187]. Mirtazapine has a faster onset of action compared with to SSRIs[188,189]. Case reports suggested a positive effect of mirtazapine on auditory[190] and visual[191] hallucinations in patients with PD and persistent psychosis without worsening motor symptoms. This antipsychotic effect of mirtazapine was attributed to 5HT-2A and/or 5HT-2C antagonism leading to dopamine release[190].

Venlafaxine

Venlafaxine is a serotonin and SNRI[144]. Venlafaxine has a rapid onset of clinical action (one week or two). In the treatment of in-patients with major depression venlafaxine was superior to fluoxetine[192]. It is used to treat melancholia (endogenous depression) and treatment-refractory depression[128]. Remission rates were significantly higher with venlafaxine than with an SSRI[193]. A single-blind study in elderly patients suffering from resistant major depression, found venlafaxine to be significantly superior to paroxetine in improving depression[194]. Adverse effects of the drug include nausea, somnolence, insomnia, and dizziness, constipation, sweating, nervousness, and abnormal ejaculation, cardiac conduction changes[128]. In non-fluctuating PD patients with depression, venlafaxine treatment for 8 wk improved depression without changes in UPDRS scores[195]. In a randomized, double-blind, placebo-controlled trial in depressed PD patients, venlafaxine extended release was effective in improving depression. The mean 12-wk reductions in depression score were 6.2 points for paroxetine group and 4.2 points for venlafaxine extended release[173].

Atomoxetine

In subjects with PD and depression, treatment with the SNRI atomoxetine was not found efficacious in relieving depressive symptoms. Global cognitive performance and daytime sleepiness, however, significantly improved[196].

Duloxetine

Duloxetine is a serotonin and noradrenaline reuptake inhibitor. In an open-label study in PD patients with major depression, duloxetine 60 mg once daily significantly improved depression scores and activities of daily living without worsening rigidity or tremor[197].

Table 4 lists selected studies on the effect of SSRIs and other antidepressant drugs on depressive symptoms in subjects with PD.

NON-PHARMACOLOGICAL TREATMENT MODALITIES

Neurostimulation

Electrical neurostimulation techniques include deep brain stimulation (DBS) of subthalamic motor nuclei or globus pallidus internus, transcranial magnetic stimulation (TMS), and electroconvulsive therapy.

Table 4 Studies on the effect of antidepressant drugs on depressive symptoms in Parkinson's disease subjects with depression

Drug	Study design	Sample size	Study objectives	Outcomes	Adverse effects	Ref.
Fluoxetine		23	Effects of fluoxetine (up to 40 mg/d) on motor performance	20/23 patients experienced no worsening of parkinsonism		[167]
Fluoxetine, fluvoxamine, citalopram, and sertraline	Open-label prospective study	62 depressed patients with PD (without dementia or motor fluctuation) (15 patients received citalopram, 16 fluoxetine, 16 fluvoxamine, and 15 sertraline)	Effects of SSRIs on motor performance and depressive symptoms	↓↑ UPDRS scores Significant improvements in depression with all SSRIs		[168]
Fluoxetine/ amitriptyline	Randomized study	77 patients with PD (37 received fluoxetine and 40 received amitriptyline)	Comparing fluoxetine (20-40 mg/d) and amitriptyline (25-75 mg/d) at low doses on depressive symptoms	Amitriptyline better controlled depression at 3, 6, 9 and 12 mo, respectively	15% abandoned amitriptyline because of side effects	[137]
Fluoxetine	Prospective, controlled, open-label study	18 patients with PD and mild depression without dementia	Influence of fluoxetine (20 mg/d) on motor functions	Significant improvements in scores of depression and Parkinson's disability		[174]
Paroxetine			To assess the tolerability of paroxetine (20 mg once per day)	Improved depression UPDRS scores ↓↑	Reversible worsening of tremor in one patient	[171]
Paroxetine		65 outpatients with PD and depression	To assess the tolerability of paroxetine (10-20 mg once per day)	Improved depression	20% stopped paroxetine because of adverse reactions Increased "off" time and tremor in 2 patients (reversible)	[170]
Paroxetine CR/ nortriptyline	Randomized, placebo controlled trial	52 patients with PD and depression	To evaluate the efficacy of paroxetine CR and nortriptyline in treating depression	Nortriptyline was superior to placebo for the change in depressive scores Paroxetine CR was not		[140]
Paroxetine/ venlafaxine	Randomized, double-blind, placebo-controlled trial	115 subjects with PD	To compare efficacy and safety paroxetine and venlafaxine extended release in treating depression in PD	Both paroxetine and venlafaxine XR significantly improved depression UPDRS scores ↓↑		[173]
Citalopram		46 non-demented patients with PD. 18 depressed and 28 non-depressed	Effect of citalopram on motor and nonmotor symptoms of depressed and nondepressed patients with IPD	Improvement in mood in 15/16 patients Motor performance ↓↑ Improved bradykinesia and finger taps in patients with and without depression		[169]
Citalopram	Prospective, open label trial	10 patients with PD and major depression, without dementia	Effects of citalopram on depressive symptoms	Significant improvement in depression and in anxiety symptoms and functional impairment		[175]
Escitalopram	Open-label study	14 Parkinson's disease patients with major depression	Effects of escitalopram on depressive symptoms	↓ in depressive symptomatology score (response and remission rates were only 21% and 14%)		[176]
Sertraline	Open-label pilot study	15 patients with PD and depression	To evaluate the safety and efficacy of sertraline to treat depression in PD	Significant improvement in depression UPDRS scores ↓↑	Side effects in 1/3 2 patients discontinued sertraline	[177]
Sertraline		54 PD patients with depressive disorders	Comparing efficacy of sertraline in the usual formulation and in the liquid oral concentrate	Improved depression on both formulations Improved clinical global impression-severity of illness scale		[179]
Sertraline		374 PD patients with depressive symptoms	Long-term effects of sertraline on motor status	Improved UPDRS ↓ Anxiety ↓ Depression	8% discontinued medication for adverse events (gastrointestinal) Worsening of tremor in some patients	[178]

Sertraline/ amitriptyline	Prospective single-blind randomized study	31 patients with PD and depression	Assessment of the effect of sertraline (50 mg) or low-dose amitriptyline (25 mg) on depression and quality of life	↓ Depression by both drugs Sertraline improved quality of life ↓↑ UPDRS scores		[138]
Sertraline/ pramipexole	Randomized trial	67 outpatients with PD and major depression but no motor fluctuations and/or dyskinesia	To compare pramipexole with sertraline	Both sertraline and pramipexole improved depression Pramipexole caused more recovery compared to sertraline (60.6% *vs* 27.3%) Pramipexole improved UPDRS motor subscore	14.7% withdrew from the sertraline group	[99]
Nefazodone/ fluoxetine	A pilot randomized trial	Depressed patients with PD	To assess the effect of nefazodone on extrapyramidal symptoms in depressed PD patients	Nefazodone significantly improved UPDRS score Both nefazodone and fluoxetine were equally effective in treating depression		[185]
Trazodone	Randomized trial	20 PD patients with and without depression	To test the ability of trazodone to improve depression and motor function	Significantly improved depression Improves motor function in depressed patients		[186]
Venlafaxine	Prospective study	14 non-fluctuating PD patients with depression	To investigate the therapeutic efficacy of venlafaxine	Improved depression scores UPDRS scores ↓↑		[195]
Atomoxetine, a SNRI	Randomized placebo- controlled study	55 subjects with PD depression atomoxetine or placebo	To assess efficacy of atomoxetine (80 mg/d) in treating depression	Failed to improved depression Improved global cognition Improved daytime sleepiness		[196]
Duloxetine	Non-comparative, open-label, multi-center study	151 patients	To evaluate the tolerability, safety, and efficacy of duloxetine 60 mg once daily in PD patients with major depressive disorder	Improved depressive scores Improved activities of daily living Tremor ↓↑ Rigidity ↓↑	8.6% discontinued the study due to side effects	[197]

PD: Parkinson's disease; SNRI: Selective norepinephrine reuptake inhibitor; UPDRS: Unified Parkinson's disease Rating Scale.

DBS surgery

This involves inserting microelectrodes into the basal ganglia nuclei, *e.g.*, subthalamic nucleus or globus pallidus internus. In advanced stage PD, deep brain stimulation of subthalamic nucleus improves motor function, motor fluctuations, dyskinesia, activities of daily living, quality of life and allows dopaminergic treatment reduction or withdrawal in a subset of patients[198-206]. Improvement in anxiety, depression, and fatigue has also been reported following subthalamic stimulation[199,200,202,206-208]. In addition, patients with severe PD subjected to bilateral subthalamic nucleus DBS were reported to have had significantly longer survival[209]. The effect of subthalamic DBS on depression, however, might not be maintained. In one study, motor UPDRS-III scores decreased within 18 mo postoperatively compared with preoperative and the medication control group. Self-Rating Depression Scale and Hamilton Rating Scale for Depression decreased within 6 and 3 mo postoperatively, respectively[202]. Cognitive deterioration[203,207,210], decline in verbal fluency and in abstract reasoning, episodic memory and executive function[211], depression[202,205,212,213], apathy[212], worsening of apathy[214] as well as the unmasking of previous psychiatric problems[215] might complicate the procedure. The increase in affective-cognitive symptoms of depression after DBS might reduce the procedure-induced motor improvement[213]. Suicide has also been reported among patients undergoing subthalamic nucleus DBS, despite clear motor improvements[213,216]. Other studies, however, reported no increased risk for suicide ideation and behaviors among PD patients subjected to subthalamic nucleus or globus pallidus interna DBS surgery[217]. Operative complications include infection, intracerebral hematoma, chronic subdural hematoma, electrode fracture, and incorrect lead placement, phlebitis, and pulmonary embolism[204,205,218].

TMS

Brain stimulation with TMS is a noninvasive approach of electrically stimulating neurons in the human cerebral cortex that is capable of modifying neuronal activity both locally and at distant sites[219]. The technique of TMS involves the passage of an electrical current through a copper-wire coil placed on the scalp. A brief, rapid time changing magnetic field is created at the level of the

coil which then induces a small electrical current in the underlying brain. Depolarization of neuronal membranes and generation of action potentials follows. In repetitive TMS (rTMS), repeated electrical pulses are generated in the cortex[220,221]. Repetitive TMS of the left dorsolateral prefrontal cortex was approved for the treatment of major depression in United States in 2008[222]. The technique appears to be without side effects[222,223]. Maruo *et al*[223] observed that three consecutive days of HF-rTMS over the M1 foot area in patients with PD failed to improve depression and apathy scales, despite significant improvement in UPDRS-III compared to sham stimulation.

Electroconvulsive therapy

In PD patients with refractory psychiatric symptoms, electroconvulsive therapy (ECT) led to improvement in symptoms of psychosis and motor symptoms with no adverse effects[224]. There are case reports that ECT was successful in the treatment of severe anxiety[225], and obsessive compulsive disorder[226] in PD, depression and parkinsonism in drug-induced parkinsonism[227]. Usui *et al*[228] reported improvement of psychosis and severity of PD in eight patients with levodopa or dopamine agonist-induced psychosis. The technique has also been used to treat depression in patients implanted with DBS. Chou *et al*[229] found that ECT dramatically improved major depression with psychotic features that occurred after bilateral subthalamic nucleus DBS surgery. Nasr *et al*[230] reported the treatment of severe depression with psychotic features and the decline in physical and mental states using ECT in a patient implanted with DBS. A randomized, double-blind trial of transcranial electrostimulation in early PD, however, found no significant effect on anxiety or depression and also on motor symptoms[231].

Neurosurgical ablation techniques

Surgery, *e.g.*, pallidotomy, subthalamotomy are sometimes used to alleviate motor symptoms in advanced PD patients refractory to medical treatment[232]. Surgery still might be resorted to in some instances where DBS is contraindicated or following complications necessitating removal of the implanted device[233]. In one study, lasting improvement in depression and apathy and no cognitive deterioration were reported in patients with advanced PD subjected to simultaneous bilateral subthalamotomies[234]. In another study, advanced PD subjects with depressed mood subjected to left-posteroventral pallidotomy performed worse on measures of verbal list learning and story recall when compared to non-depressed subjects or right-posteroventral pallidotomy subjects with depressed mood[235].

Cognitive behavior therapy

This psychotherapeutic treatment option improves comorbid depression and anxiety and the quality of life in PD patients[236,237]. In one study, patients on cognitive behavior therapy reported greater reductions in depression scores, anxiety, and improved quality of life compared with the clinical monitoring group[238]. Cognitive behavior therapy delivered *via* telephone to persons with PD also proved useful in improving psychiatric symptoms[239].

Insight from animal studies

The use of animal models of PD has greatly enabled our understanding of the pathogenetic mechanisms of depression in PD and also helped to identify potential therapeutic targets. Many studies employed the neurotoxin 6-hydroxydopamine (6-OHDA) which when injected into the striatum of rats induces marked depletion of dopamine, serotonin and also noradrenaline in the striatum[240]. Using this model, Tadaiesky *et al*[241] demonstrated that anxiogenic- and depressive-like behaviors occur early in the course of experimental parkinsonism analogous to that in early phases of human PD. This occurred along with alterations of dopamine, serotonin and noradrenaline in the striatum. Mild anxiogenic effects were also reported in 6-OHDA-lesioned rats. These effects were not amenable to treatment with L-dopa[242]. Branchi *et al*[243] found depressive-like behavior but reduced anxiety and a marked change in social behavior and no learning or memory difficulties in 6-OHDA-lesioned rats. Courtière *et al*[244] using the reaction time task test provided data that 6-OHDA lesioned rats had cognitive impairment similar to PD patients. These studies indicated that behavioral changes also occur in early phases of experimental PD. Studies in rodents also allowed the evaluation of such techniques as, TMS, rTMS and DBS. Thus high-frequency electrical stimulation of the subthalamic nucleus in rats was shown to increase striatal dopamine efflux, thereby indicating that the benefit from this technique is probably due to enhanced dopamine release within the basal ganglia[245]. Extracellular levels of 5HT in both striatum and medial prefrontal cortex also decreased following high-frequency electrical stimulation of the subthalamic nucleus even in dopamine-denervated rats. Changes in 5HT neurotransmission might therefore account for the depression seen in some patients following DBS of the subthalamic nucleus[246]. Ghiglieri *et al*[247] found that rTMS increases striatal excitability and rescues corticostriatal long-term depression in experimental parkinsonism in rats.

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MINIREVIEWS

Rituximab in neuromyelitis optica: A review of literature

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Abstract

Neuromyelitis optica spectrum disorders, or neuromyelitis optica (NMO), is an autoimmune disease of the central nervous system that must be distinguished from multiple sclerosis. Therapeutic approaches to relapse prevention in NMO include immunosuppressants and monoclonal antibodies. Rituximab, a monoclonal antibody that targets CD20 antigen expressed on the surface of pre-B, mature B-lymphocytes and a small subset of T-lymphocytes, has been widely used for the treatment of NMO. In this review, we aim to summarize global experience with rituximab in NMO. We identified 13 observational studies that involved a total of 209 NMO patients treated with rituximab. Majority of rituximab-treated patients evidenced stabilization or improvements in their disability scores compared to pre-treatment period and 66% of patients remained relapse-free during treatment period. Monitoring rituximab treatment response with CD19+ or CD27+ cell counts appears to improve treatment outcomes. We offer clinical pointers on rituximab use for NMO based on the literature and authors' experience, and pose questions that would need to be addressed in future studies.

Key words: Neuromyelitis optica; Rituximab; Longitudinally extensive transverse myelitis; Optic neuritis; CD19+; CD27+

Core tip: Relapsing neuromyelitis optica (NMO) is an autoimmune disorder of the central nervous system that often results in severe disability and death if untreated. Rituximab, an anti-CD20 monoclonal antibody, appears to be a promising treatment option for NMO. In this review, we summarize the results of 13 observational studies that assessed efficacy of Rituximab in neuromyelitis optica. On average, 66% of patients remained relapse-free during treatment period and in the majority of patients disability scores have stabilized or improved. Monitoring response to rituximab with CD19+ and CD 27+ cell counts appears to improve outcomes.

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INTRODUCTION

Neuromyelitis optica spectrum disorders, hereafter

referred to as "Neuromyelitis optica (NMO)", is an autoimmune disease of the central nervous system (CNS)[1]. Diagnostic criteria for NMO have undergone several revisions in recent years, but core clinical syndromes - longitudinally extensive transverse myelitis and optic neuritis, have been retained. The most recent iteration of the diagnostic criteria for NMO is based on International Panel for NMO Diagnosis consensus paper[2]. In Aquaporin-4-IgG (AQP4-IgG) seropositive patients, diagnosis can be made after a single NMO-compatible relapse. AQP4-IgG seronegative NMO criteria include evidence of dissemination in space as well as at least one well-recognized syndrome of NMO, such as ON, LETM or intractable vomiting/hiccups[2].

NMO has been reported worldwide with prevalence ranging from 0.52-4.4/100000[3]. In Western counties, NMO is rare relative to multiple sclerosis (MS) - ratio of 1:50-100[4-6], but in the developing counties, NMO may constitute up to 40% of all CNS autoimmune diseases[7]. Prognosis and treatment in NMO and MS are different. Five-year mortality of untreated relapsing NMO was 68% - a much higher rate than in MS - and half of the surviving patients had permanent monoplegia or paraplegia[8]. Disease modifying therapies for relapsing MS, such as Interferon and the remarkably effective Natalizumab, fail to prevent, and may even precipitate, relapses of NMO[9,10]. Current strategies for relapse prevention in NMO include immunosuppressants and monoclonal antibodies[11,12], but efficacy of these approaches has not been tested in randomized clinical trials. One of the most promising agents for NMO is rituximab (RTX), a monoclonal antibody that targets CD20 antigen expressed on the surface of pre-B, mature B-lymphocytes (but not normal plasma cells)[13] and a small subset of T-lymphocytes[14]. Our review aims to summarize global experience with RTX for the treatment of NMO and offer clinical pointers based on the literature and authors' experience.

RATIONALE FOR B-CELL DEPLETING THERAPY IN NEUROMYELITIS OPTICA

Landmark pathologic study by Lucchinetti *et al*[15] concluded that "the pronounced Ig reactivity co-localizing with complement activation at sites of vessel damage may be due to a specific antibody targeted to a vascular antigen"[15]. This prediction was borne out two years later when Lennon *et al*[16] discovered an exquisitely NMO-specific autoantibody directed against AQP-4, a water channel found in astrocytic end-feet[16]. Current conceptualization of NMO pathogenesis is that anti-AQP4 auto-antibody binds to AQP-4[17] and initiates complement-mediated astrocyte injury and inflammatory reaction that secondarily affects oligodendrocytes and leads to demyelination and neuronal loss[18]. This hypothesis successfully explains many features of NMO, but does not account for the diversity of observed pathologic findings[19], nor for disease pathogenesis in anti-AQP4- Ab seronegative NMO patients, who comprise approximately 30% of NMO cases in the United States[5].

In view of the central role of humoral autoimmunity to NMO pathogenesis, it is not surprising that B cell lineage depletion would be proposed as a rational therapeutic strategy. Indeed, shortly after discovery of anti-AQP-4 Ab, Cree *et al*[20] reported an open label study of RTX in NMO that demonstrated high efficacy of the drug in all but one of their patients. A number of reports on RTX efficacy in NMO from different parts of the globe have since appeared. This review included all English-language studies that involved 5 or more RTX-treated NMO patients and recorded either relapse rate/number before and after treatment with RTX, or expanded disability status scale (EDSS) scores before and after treatment with RTX, or both outcome measures. We searched PubMed for "Neuromyelitis Optica" and "Rituximab" and cross-checked references. We identified 25 articles and finally 13 articles were included in this study, which met our inclusion criteria. Two articles were excluded for multiple treatments used; four were excluded for other diseases included; four were excluded for having less than 5 patients; and another two articles were excluded for not documenting treatment effect. Two unpublished case series of RTX-treated NMO that were presented at recent international neurologic conferences were also included in this review; additional data was obtained from the authors[21,22].

EFFICACY OF RTX IN NMO

Thirteen studies met our inclusion criteria. The total number of treated patients was 209, of whom the overwhelming majority were women (approximately 90%). Table 1 summarizes demographic and clinical data from the 13 studies. Four out of the thirteen studies reported median annualized relapse rate (ARR) before and after RTX[20,23-25]. Median ARR prior to treatment ranged from 1.7-2.6 and it decreased to 0-0.4 during the treatment period, which was usually 1-2 years. Two studies reported change in mean ARR[26,27], which decreased from 1.2-2.4 pre-treatment to 0-0.3 after treatment was started. The remaining seven studies specified total number of relapses before and after RTX as detailed in Table 1[21-22,28-32]. In 11 out of 13 studies, 48%-75% of patients were relapse-free during treatment period. There were two exceptions: in the study by Lindsey *et al*[32] only 3 out of 9 patients (33%) were relapse-free; this study was critiqued for possible under-dosing of RTX[33]. In the study of Yang *et al*[28] none of the 5 patients experienced any further relapses while on RTX.

In all but one study, some patients "failed to respond" to treatment. Javed *et al*[22] characterized nearly 33% of their NMO patients as "non-responders" based on the fact that RTX failed to delay further relapses, which occurred within 2.5 mo post treatment[22] (Table 1). Phenomenon of disease rebound in the immediate post-

Table 1 Case series of rituximab in neuromyelitis optica

Ref.	Country; Type of study	No. of patients (n = 209)	Mean age at RTX; % Female	% Anti-AQP4 Ab seropositive	RTX Protocol /treatment duration	ARR before RTX	ARR after RTX	% Relapse-free	EDSS (median) before --> after RTX
Cree *et al*[20]	United States; Retrospective	8	37[1]; 88%	N/A	A- treatment B- retreatment	2.6 (median)	0 (median)	75% (6/8 pts at 12 mo f/u)	7.5--> 5.5
Jacob *et al*[23]	United States/ England; Retrospective	25	43[1]; 88%	70%	A or B; median interval between cycles-8 mo 19 mo follow up	1.7 (median)	0 (median)	72% (17/25 at 12 mo estimated)	7--> 5 2 patients deceased
Bomprezzi *et al*[31]	United States; Retrospective	18	46 (+/-12); 83%	67%	B	15 pts-RTX tx and 7 had relapses. 42% (5/12) showed "positive treatment effects", the other 7 continued to relapse despite RTX therapy		53% (8/15)	Severe disability from NMO' - 10 patients
Bedi *et al*[24]	United States; Retrospective	23	46[1]; 91%	72%	A or B; 32.5 mo	1.87 (median)	0 (median)	74 % (17/23 pts)	7--> 5.5
Pellkofer *et al*[30]	Germany; Prospective	10	47[1]; 90%	100%	B; number of cycles of RTX 1-5	Ever before RTX: 1.3 mo, 12 m before RTX: 2.4 mo, 24 m before RTX: 1.72 mo, With RTX: 0.93 mo		50% (5/10 at 12 mo estimated)	6--> 6.5[1] 1 patient deceased
Javed *et al*[22]	United States; Retrospective	15	34; N/A	N/A	B; patients were given RTX 1g x1 usually 6-9 mo after the initial dose	2/10 had 2 relapses in 6 mo post RX. 5 non-responders had mean of 1.45 (median 1) relapses in mean 12.2 (median 10) mo		67% (RTX delayed further relapses for 9 mo or more)	N/A
Gredler *et al*[26]	Austria; Retrospective	6	38; 83%	66%	375 mg/m^2; no of infusions 3-16 (mean = 6.67), interval between infusions 3.3-11 mo	2.5 (mean)[1]	0.4 (mean)[1]	67% (4/6)	5.25--> 2.25[1]
Ip *et al*[25]	China; Prospective	7	52; 85%	66%	A or B: Mean # trx courses: 2.85. median 2	Mean ARR = 2.4 median ARR = 2[1] 5 became relapse free. 2 had 50% reduction over median 24 mo		71 % (5/7)	8--> 7
Lindsey *et al*[32]	United States; Retrospective	9	N/A; 89%	60%	A or B: Mean duration: 74.2 mo	3 pts with early relapses in first month after RTX, 4 pts (including 1 pt with early relapse) with later relapses		33% (3/9)	3.5--> 4.3[1]
Kim *et al*[27]	South Korea; Retrospective	30	38.4 (± 10.5); 90%	77%	A or B; mean 61 mo (range 49-82 mo), median 60 mo	2.4 (mean)	0.3 (mean)	70% (21/30 at 2 yr f/u)	4--> 3
Yang *et al*[28]	China; Prospective	5	42[1]; N/A	80%	100 mg (50-59 mg/m^2) RTX IV 1 dose/wk for 3 cons wk; mean duration: 12.2 mo	1.16[1] (mean)	0[1] (mean)	100%	4.5--> 4
Mealy *et al*[29]	United States; Retrospective	30	45[1]; 83%	50%	B; median of 20 mo (range 5-83 mo)	Total pretreatment ARR- 2.89	Total post-treatment ARR- 0.33	67% (20/30)	N/A
Farber *et al*[21]	United States; Retrospective	23	38; 100%	74%	Mean of 22 mo (range 2-96 mo)		Median ARR was 0.24; mean was 1.02 (SD = 1.36)	48% (11/23)	N/A

[1]Estimated based on results table or manuscript when possible. A or B (in RTX protocol column): There were two treatment protocols used- Protocol A with 4 doses RTX 375 mg/m^2 IV wk for 4 wk; Protocol B with 2 doses of RTX 1000 mg IV 2 wk apart. NMO: Neuromyelitis optica; ARR: Annual relapse rate; EDSS: Expanded disability status scale; RTX: Rituximab; AQP4: Ab - aquaporin 4 antibody; N/A: Not available.

induction period was documented by Perumal *et al*[34] in 6 out of their 17 patients; however most patients with

post-induction relapses evidenced disease stabilization with further RTX dosing and so need not be necessarily classified as "true non-responders". Perumal *et al*[34] hypothesized that cytokine release and increases in BAFF and AQP4 levels that immediately follow RTX infusion[35] may precipitate a post-infusion relapse in highly active NMO patients.

Continual disease activity can occur in RTX-treated NMO patients with complete depletion of B cells[29,30,32,36]. Risk factors that would predict non-responsiveness to RTX are presently unknown. It was suggested that RTX non-responders may require not only B-lymphocyte elimination with RTX, but an additional, "broad-spectrum immune-suppressant" to achieve disease remssion[31]. This strategy has been successfully adopted in the treatment of Rheumatoid Arthritis, where RTX is often combined with Methotrexate or Cyclophosphamide[13]. We discuss potential mechanisms that may explain lack of response to RTX in "Variability in responses to RTX treatment" section below.

EDSS scores before and after RTX were reported in 9 out of 13 studies. In 7 of the 9 studies, EDSS at last follow-up was lower than prior to RTX initiation. Exceptions were the studies by Lindsey *et al*[32] and Pellkofer *et al*[30], in which EDSS at last follow-up increased by 0.8 and 0.5, respectively, compared to pre-treatment EDSS[30,32].

ADVERSE EVENTS

Two studies recorded fatal outcomes in RTX-treated NMO patients. In the study of Jacob *et al*[23], one patient died from a brainstem NMO relapse and another succumbed to suspected septicemia. Pellkofer *et al*[30] reported one death due to presumed cardiovascular failure that occurred 3 d after a rituximab infusion.

Adverse events were not systematically documented across the studies, so estimates of their prevalence are not possible. A number of infections have been observed - mostly, herpetic rashes and tuberculosis reactivation. RTX treatment carries a small risk of progressive multifocal leukoencephalopathy (PML) - 1 case per 25000 individuals in one large cohort of patients with rheumatoid arthritis[37]. No cases of PML in RTX-treated NMO patients have been reported to date, though there was a single case report of PML in NMO patients treated with azathioprine[38]. Overall, adverse events profile of RTX in NMO appears to be consistent with known safety profile of the drug[13]. Infusion reaction to RTX are very common, but can usually be mitigated by pre-treatment with intravenous steroids anti-histamine and slow titration of RTX.

DOSING OF RTX AND BIOMARKERS OF TREATMENT RESPONSE

The majority of studies used one of two "induction protocols": 375 mg/m^2 IV once a week for four consecutive weeks ("protocol A" in Table 1), or 1000 mg IV infused two weeks apart ("protocol B"). Timing of subsequent doses either followed a fixed schedule - with typical time to the next infusion cycle of 6-9 mo or was based on monitoring parameters. The most commonly used test for monitoring B cell suppression was CD19+ count assessed by flow cytometry. Since RTX interferes with the direct analysis of CD20 cell surface antigen *via* flow cytometry due to its mechanism of action, CD19+ antigen, which is largely co-expressed with CD20, is used as a surrogate marker to assess extent of B cell depletion[26]. However, CD19+ count may also overestimate degree of B cell depletion[39]. RTX typically depletes CD 19+ counts to undetectable levels (< 10 cells per μL) within 2-4 wk of infusion[13].

Table 2 summarizes the use of biomarkers to monitor treatment response to RTX in NMO. Several studies showed that CD19+ B cell population greater than 1% of lymphocyte total is a risk factor of a relapse. Farber *et al*[21] measured CD19 counts post-relapse and during periods of stability, and noted higher B cell counts in the immediate post-relapse period. Yang *et al*[28] suppressed CD19+ count to less than 1% in all their patients and were able to achieved complete eradication of relapses, despite lower doses of RTX used[27]. Pellkofer *et al*[30] used monthly, highly sensitive flow cytometry measurements to demonstrate that complete B cell suppression led to sustained clinical stabilization in most patients. Bomprezzi *et al*[31] showed that B cells become undetectable within 2 wk of the first dose of RTX, but rise to 2%-12% at the time of a relapse[31]. The early rise in CD19+ cells correlated with radiologically proven relapses, and 5 out of 7 patients experienced a relapse when CD19+ B cell population exceeded the 1% threshold[31]. In summary, preponderance of evidence favors suppressing CD19+ B cell to ≤ 1% of the total lymphocyte count in NMO patients for maximal efficacy.

Efficacy of "low dose" RTX on CD19 counts was assessed in two studies. Yang *et al*[28] used RTX 100 mg infusion once a week for 3 consecutive weeks, which was followed by the next RTX 100 mg dose when CD19+ cells were > 1% and the memory CD19+ CD27+ B cells were > 0.05%. In this regimen, CD19+ cells started to increase in 4 of the 5 patients approximately 140 d after the initial RTX infusion, necessitating a re-infusion[28]. In the Greenberg *et al*[40] study, RTX 100 mg dose resulted in early re-population of B cells compared to the 1000 mg dose[40]. The median number of days for CD19 population to reach threshold of 2% was 133 d in the 100-mg per dose arm *vs* 259 d in the 1000-mg per dose arm[40].

Kim *et al*[27] proposed that CD27$^+$ memory B cells may be a more relevant biomarker of pathogenic B cells depletion in NMO than CD19+ B cells[26]. Memory B cells can elicit larger and faster responses to antigen than naive B cells, and so may be more relevant to disease pathogenesis. Re-emergence of CD27+ memory B cells above the therapeutic target (< 0.05% of PBMCs) may occur even when CD19+ B cells levels were < 0.5% of

Table 2 Monitoring parameters in Neuromyelitis optica patients treated with rituximab

Ref.	Monitoring parameter/comments
Cree *et al*[20]	CD19 levels- when detectable, patients were re-treated. CD 19 followed bimonthly. 2 protocols-planned infusions every 6 mo or 12 mo
Jacob *et al*[23]	CD19 not routinely monitored. Some RTX given when B-cell counts detectable either 6 or 12 mo in intervals or when CD19+ became detectable
Bomprezzi *et al*[31]	Flow cytometry used to test circulating B cells. Suggest clinical relapses occurring while on RTX therapy correlate with reconstitution of circulating B cells. Correlated that even early rise in CD20+ cells correlated with radiologically proven relapses. B cells had re-sent between 2% and 12% at time of new attack. Total of 7 patients relapsed after RTX-5 had acute event when B cell counts just returned to greater than 1%, whereas 2 patients continued to relapse despite B cells being undetectable. Detected significant variability in timing of reconstitution of normal values, which implies that scheduling of doses of RTX can be adjusted accordingly
Bedi *et al*[24]	CD19 cell counts planned every 2-3 mo, but not collected systematically for report
Pellkofer *et al*[30]	Measured lymphocyte subsets by flow cytometry; B cell depletion defined as counts below 0.01×10^9 /L. B cells became undetectable in 9 out of 10 patients within 14 d after 1st dose. Time of B-cell repopulation varied. After 3 patients experienced a relapse shortly after reappearance of B cells, RTX given at fixed interval every 6 to 9 mo, which this led to improved outcomes
Javed *et al*[22]	"Non-responders" were defined as clinical attack < 6 mo post rituximab treatment, when B cell count was still undetectable
Gredler *et al*[26]	Flow cytometry used; B cells quantified using following combinations of monoclonal antibodies: CD3/19/45, 19/27/45, 19/38/45. Two patients out of 6 had relapses while B-cells were absent
Lindsey *et al*[32]	4 patients had relapses after more than 1 mo when peripheral B cell count "very low". Case 1: CD19 increased to 250 cells/μL had sensory relapse, no further symptoms for 18 mo; Case 2: Had relapses with CD19 count of 0; Case 3, 4, 6 no further relapses; Case 5: CD19 1 cells/μL at 10 mo, 12 cells/μL at 13 mo and subsequent relapses; Case 7--continued to have relapses with 1 cell/μL at 7 mo, 4 cells/μL at 12 mo. Case 8: CD19 count 3 cells/μL, with continued relapses; Case 9: continued relapses with CD19 1 cells/μL
Kim *et al*[27]	Blood samples obtained every 6 wk in 1st year, every 8 wk in second year. Therapeutic target for CD 27+ memory B cell depletion was less than 0.05% of PBMCs. Patients received additional infusion of 375 mg/m^2 if frequency of re-emerging memory CD27+ B cells in PBMCs exceeded 0.1% by flow cytometry. CD 19 B cells counts measure- less than 0.01×10^9 /L or less than 0.5% of PBMCs (considered B cell depletion in prior studies. 60%-65% relapses occurred when CD19 were depleted. Authors argue CD27+ more informative biomarker than CD19
Yang *et al*[28]	Goal of CD19+ B cells to less than or equal to 1%, as well as CD19 CD27 B cells to less than or equal to 0.05% of PBMCs. All with no relapses despite low doses of RTX (100 mg single infusion and follow up infusion at mean of 35 wk)
Mealy *et al*[29]	CD19 cell counts tested monthly, repeated dosing scheduled on detection of CD19 greater than 1% of total lymphocyte population or at regular 6 mo intervals
Farber *et al*[21]	Total of 23 relapses, of which 70% occurred when B cells < 1% of lymphocytes. 7 relapses (30%) occurred when B cells greater or equal to 1% of lymphocytes. CD19 > 1% was associated with higher rate of relapses

RTX: Rituximab.

PBMCs. Perhaps, presence of memory cells in patients with ostensible absence of CD19+ cells can be explained by a recent study in which loss of CD19 surface antigen from healthy donor B cells exposed to rituximab *in vitro* was not necessarily associated with B cell death[41]. In the study of Kim *et al*[27], no relapses were observed in 29 out of 30 patients in whom CD27+ memory B cell fraction was below the therapeutic target. This important finding is corroborated by the small series of Yang *et al*[28], cited above. More studies are needed to determine if CD27+ should replace CD19+ as the biomarker of choice in monitoring response to RTX in NMO.

Pellkofer *et al*[30] studied utility of AQP4-Ab, total B cell counts and B cell fostering cytokines, such as BAFF (B cell activating factor) or APRIL (a proliferation-inducing ligand) as biomarkers in NMO. They found that disease activity correlated with B cell depletion, but not with AQP4-Ab or APRIL levels[30]. Relationship between CD19 counts and Anti-AQP4 titers was analyzed by Jarius *et al*[17], who concluded that administration of RTX was followed by a "prompt and marked decline" in AQP-4 Ab, though the auto-antibody remained detectable in nearly all patients[17].

VARIABILITY IN RESPONSES TO RTX TREATMENT

The mechanisms responsible for variability in RTX treatment responses are unclear. An early, post-infusion relapse may be related to incomplete elimination of pathologic B cells as well as transient increase in B cell activating factor, anti-AQP4 Ab titers and other cytokines following infusion[34]. Greenberg *et al*[40] reported an NMO patient who was "resistant" to RTX: after an initial fall of CD19 cell count to 0, patient continued to experience clinical relapses and marked early return of B cells at 91 d after RTX, which could not be suppressed by further doses of RTX. This appears to be an exceptional case, as most "true" non-responders in the Greenberg *et al*[40] study - 6 out of 8 - had CD19 count below 2% at the time of relapse. Kim *et al*[27] also noted that 13 out of 20 relapses (65%) occurred even when CD19 B cell fraction was less than 0.5% PBMCs[27]. Lindsey *et al*[32] ask whether in patients with continued relapses despite complete B cell suppression, pathogenic T-cell may play a relatively more prominent role in pathogenesis. It is also possible RTX does not completely eliminate pathogenic clones in the periphery

or that CD19+ count overestimates the degree of peripheral B cells depletion[41]. Furthermore, peripherally administered monoclonal antibodies have limited penetration across the blood-brain barrier - typically CSF concentration is < 0.1% of serum antibody concentration[42]. Although CSF Rituximab concentration may be considerably higher if blood-brain barrier is perturbed[39], its concentration may still be insufficient for elimination of B cells from CSF.

CONCLUSIONS AND QUESTIONS FOR FUTURE STUDIES

Thirteen observational studies from across the world (Table 1) have documented stabilization or improvement in disability scores in a majority of NMO patients upon initiation of RTX. Pooling data across the studies shows that 66% of patients were relapse-free throughout the treatment period (typically 1-2 years). It is possible that with a more rigorous monitoring of response with CD19+ or CD27+ biomarkers and improved strategies to avoid relapses in the post-induction period even more impressive results could be achieved. Although the studies in our review have been uncontrolled and mostly retrospective and so subject to various biases (*e.g.*, ascertainment bias, selection bias, publication bias), they are consistent in demonstrating robust treatment response. Considering the natural history of untreated NMO[8], it would seem highly unlikely that the observed reduction of relapses and improved disability scores in RTX-treated patients is accounted for solely by artifacts of data collection or regression to the mean. The accumulated weight of evidence, in authors' opinion, casts doubt on the possibility of genuine clinical equipoise in NMO at the present time.

Important questions remain with regard to place of RTX in the treatment algorithm of NMO. A recent retrospective review concluded that RTX had the lowest failure rate compared to the commonly used oral immunosuppressants[5]. Based on this data, and overall efficacy of RTX in the published studies, RTX should be strongly considered in any NMO patient who continues to relapse on oral immunosuppressants[13]. The question of whether RTX should replace prior treatment or be combined with it remains unresolved. Combination therapies, in wide use for rheumatologic diseases, have not received sufficient attention in neuro-immunology and will need to be studied more in the future. An acute treatment often used during NMO relapse is plasma exchange (PLEX)[43]. Efficacy and safety of PLEX in other refractory systemic autoimmune disease have been shown in several studies[44,45] and its role as maintenance therapy of NMO is currently being investigated[46].

Should RTX be the agent of choice for all previously untreated patients with NMO? The authors would consider RTX as a first-line therapy in a patient with aggressive disease course as well as in the older NMO patients, who tend to have worse outcomes[47]. It is less clear whether risk-to-benefit ratio calculation would favor RTX in milder and earlier cases, *e.g.*, in an AQP4-Ab seropositive patient after single relapse.

What would be the optimal timing for initiating RTX? If, as suggested by some studies[22,32,34], RTX could exacerbate NMO in the immediate post-infusion period, it would probably be safer to initiate RTX after a period of stability rather than during an acute exacerbation. This question requires further study as the data is conflicting. When switching a patient to RTX, a prudent recommendation is to avoid discontinuing prior therapy prematurely, as delay in starting RTX could put the patient at risk of relapse[24]. In our practice, we routinely continue treatment with an oral immunosuppressant for at least one month after RTX is started. With regard to timing of repeat RTX cycles, the literature supports use of CD19+ and, possibly, CD27+ cell count, to monitor treatment response (Table 2). One goal of treatment should be to keep these counts below threshold levels.

Important questions remain regarding long term safety and efficacy of RTX, and duration of therapy. There is little data with regard to long-term safety of RTX in NMO, but the long-term safety record of RTX in rheumatoid arthritis is reassuring[48]. Would it be safe, from NMO standpoint, to discontinue treatment with RTX after a (prolonged) period of stability? A recent study documented that a period of several years of no disease activity after RTX is discontinued is possible in some patients, though 2 out of 4 patients in that series experienced relapses after years of quiescence[49]. Considering the potentially devastating consequences of NMO relapse, routine discontinuation of RTX and "watchful waiting" is probably not advisable.

It is hoped that randomized clinical trials, several of which are under way now (*e.g.*,[50]) as well as multi-center collaborative observational studies based on NMO registries, such as online NMOBase registry (www.msbase.org), could provide data on long-term safety and efficacy of RTX in NMO and help resolve the unanswered questions raised in our review. Quality of observational studies in NMO could be improved by adherence to accepted guidelines[51], especially with respect to reporting outcomes (relapse rates and disability scores).

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MINIREVIEWS

Resolution of idiopathic intracranial hypertension after sustained lowering of cerebrospinal fluid pressure

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Abstract

Idiopathic intracranial hypertension (IIH) is a syndrome of headache due to raised intracranial pressure (ICP) where the cerebrospinal fluid (CSF) is normal and there is no alternative pathology on imaging. The aetiology is unknown. This review questions many of the prevailing views regarding aetiology and treatment of IIH. It explores the concept that there is a vicious cycle of fluctuating raised ICP leading to secondary compression of the transverse sinuses and further elevation of ICP. It also raises the question as to whether this vicious cycle could be relieved by prolonged drainage of CSF as seen in Lumbar puncture induced low-pressure headache or alternatively a lumbar drain.

Key words: Lumbar puncture; Cerebrospinal fluid drainage; Idiopathic intracranial hypertension; Low-pressure headache

Core tip: Resolution of idiopathic intracranial hypertension can be achieved by prolonged cerebrospinal fluid drainage as seen with Lumbar puncture induced low-pressure headache.

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INTRODUCTION

Idiopathic intracranial hypertension (IIH) also referred to as benign intracranial hypertension or pseudotumour cerebri is a syndrome of headache due to raised intracranial pressure (> 20 cm H_2O in non-obese patients and > 25 cm H_2O in obese patients) where the cerebrospinal fluid (CSF) is normal and there is no alternative pathology on imaging. Patients present with headache, with or without visual obscuration's and or various cranial nerve palsies most commonly a 6th nerve palsy. In the early stages visual acuity is normal, the blind spot is enlarged and virtually all patients have bilateral papilloedema, although rare cases have been reported where papilloedema is absent[1-3]. The major consequence of untreated or undertreated IIH is visual

loss.

AETIOLOGY OF IIH

The aetiology is unknown with many suggested causes[4-6] most of which to this author do not make sense.

To this author there is only one constant feature present in all patients with IIH and that is the presence of fluctuating raised intracranial pressure. Intracranial pressure (ICP) monitoring has demonstrated the presence of B-waves (rhythmic oscillations occurring every 1-2 min. The ICP rises in a crescendo manner to levels 20–30 mmHg higher than baseline and then falls abruptly)[7,8]. These B-waves almost certainly explain the fluctuations of CSF pressure measurements seen with a Lumbar puncture (LP) and I would like to suggest the intermittent compression of the transverse venous sinuses that King and his colleagues elegantly demonstrated is secondary to and not the primary cause of the raised ICP[9].

What triggers the initial elevation of CSF pressure is unclear. The majority (but not all) patients are obese and females of child bearing age (there are occasional reports of males affected by IIH[10]). It is feasible that the demonstrated elevation of right atrial pressure in obese individuals transmitted to the cerebral venous system[11] could be the very initial trigger[12]. If this is the mechanism then the obvious question is why does this not occur in obese males and why do non obese females develop IIH? The answer is unknown; could it be that female hormones present in premenopausal women reduce the stiffness of the venous walls and predispose them to compression? The author has not been able to find any literature to support such a hypothesis.

The fact that obesity is not present in every patient would indicate that it is not the primary cause of IIH, but increases the risk of developing this condition. There are many other suggested causes of IIH[13,14], the fact that they are not present in every patient must raise significant doubt about their primary role in the aetiology of this condition.

An identical clinical picture is seen in some patients with cerebral vein thrombosis, leading to the suggestion that obstructed venous drainage may play a role in IIH. In recent years stenting of transverse sinuses has also led to a resolution of IIH[15-19], despite the fact that it is well established that the narrowing in the transverse sinuses is secondary to the raised pressure[9]. There is one simple clinical observation that rules out transverse sinus narrowing as the cause of IIH, it not present in every patient and it is not a constant feature in patients in whom it is seen. If the transverse sinus narrowing is secondary to the raised pressure then the question is how does stenting lead to a resolution of IIH in some cases? Pickard *et al*[20] have suggested on the basis of CSF and venous sinus pressure measurements that, in many cases of IIH, there is functional obstruction of venous outflow through the dural sinuses. Raised pressure of CSF (Pcsf) partly obstructs venous sinus outflow, thereby increasing sagittal sinus pressure (pss) which, in turn, leads to a further rise in Pcsf, et sequor. They further suggest that this vicious cycle can be interrupted by draining CSF. Is it possible that stenting helps break this cycle of fluctuating ICP and intermittent venous compression, allowing venous drainage and subsequent normalisation of ICP? Supporting this concept is the observation by McGonigal *et al*[21] of resolution of IIH and transverse sinus stenosis in a patient following a lumbo-peritoneal shunt where the patient developed a low-pressure headache.

There is no consensus about what is causing the raised pressure. Logically the pressure within a closed space reflects the contents of the space and the rigidity of the wall. The skull is rigid, the ventricles are slit like, there is no collection of CSF over the hemispheres, the venous sinuses are compressed and arterial pressure is raised secondarily to the raised ICP. It therefore stands to reason that there must be increased fluid in the cerebrum.

The concept that the raised intracranial pressure is related to fluid in the interstitial space is supported by recent studies on CSF dynamics. The traditional view that the majority of CSF is produced by the choroid plexus, circulates through the ventricles and the subarachnoid space to be absorbed by the arachnoid villi has recently been challenged[22]. The CSF circulation also comprises a pulsatile to and fro movement throughout the entire brain with local fluid exchange between blood, interstitial fluid and CSF[23,24]. There is a growing consensus that the interstitial fluid and CSF are mainly formed and reabsorbed across the walls of CNS blood capillaries with aquaporins playing a role[25]. It is now believed that there is a continuous bi-directional fluid exchange at the blood brain barrier and the cell membranes at the border between CSF and the interstitial fluid spaces[24].

The total volume of CSF is estimated to be 150 mL in adults with 25 mL in the ventricles. It has also been estimated that nearly 30% of CSF production may come from the ependyma[23]. CSF production is estimated to be 0.37 mL/min or approximately 500-600 mL/d[24]. If IIH represents a vicious cycle of raised intracranial pressure due to an increase in interstitial fluid with secondary venous compression this could explain why stenting could break the cycle by abolishing the venous compression. It might also explain the observation that an uncomplicated LP would not break the cycle as CSF would re-accumulate rapidly. It could also explain how a low CSF pressure that would occur with a continuous leak of CSF in the setting of a low-pressure headache could also break the cycle. The CSF must be leaking at a greater rate than it is being produced.

TREATMENT OF IIH

There are many review articles[4,26,27] that discuss the current treatment if the initial LP fails to lead to a

resolution, treatment options include serial LP's, medical therapy (weight loss, Acetazolamide, Topiramate or Octreotide) and surgical intervention (bariatric surgery, lumbo-peritoneal drain, transverse sinus stenting or optic nerve fenestration). As Batra and Sinclair comment "the aetiology is poorly understood and there are no evidence-based guidelines on the management of the disease".

It is not the intention of this article to discuss these various treatment options in detail suffice to say that medical therapy tends to be employed for mild cases of IIH and surgical intervention for the more severe cases with a tendency to favour optic nerve fenestration if vision is threatened. Rather I would like to explore the concept of "resetting the abnormally elevated pressure to normal" by prolonged CSF drainage reflecting our own observations[28-30] and a review of the literature.

LP is used to confirm the diagnosis and occasionally a single LP[31,32] or several LP's[33] can result in resolution of IIH but how this occurs is unclear. In the study of children by Weisberg *et al*[33] 20 to 50 mL of CSF was removed each time but they did not comment on the closing pressure or the whether patients developed low-pressure headache. When serial LP's are employed the CSF pressure is reduced to a normal level, 10-20 cm H_2O. We would argue that CSF is replaced very rapidly and unless the pressure is lowered to below normal and or the CSF is drained at a rate higher than it is replaced the vicious cycle of elevated intracranial pressure cannot reverse.

In refractory cases a lumboperitoneal shunt is often recommended. These run the risk of infection and recurrence of IIH when they become occluded. The CSF is often shunted to maintain the CSF at a normal pressure and to avoid a low-pressure headache from over drainage. One case in this series developed a low pressure headache after insertion of a lumboperitoneal shunt requiring removal, following which she experienced a resolution of IIH. We suspect the reason the IIH "recurs" with blockage of the shunt is that it was never reversed in the 1st case by the shunt, but rather the CSF pressure was maintained at a level that leads to a resolution of headache and papilloedema but not low enough to reverse the excess fluid in the intracellular space.

In 2009 we observed a young non obese female with IIH who had bilateral narrowing of the transverse sinuses demonstrated on magnetic resonance venography (MRV). MRV (using the same methodology) immediately before and 15 min after the next two LPs showed partial resolution of the transverse sinus narrowing when the pressure was reduced from 50 cm H_2O to 11cm H_2O and complete resolution of the bilateral transverse sinus narrowing when the pressure was reduced from 47 cm H_2O to 8 cm H_2O[28]. On the basis that stenting can lead to a resolution of IIH, we postulated that lowering the CSF pressure lower than usually recommended, could result in a resolution of the transverse sinus narrowing and therefore a resolution of IIH. This proved not to be the case, in several patients where the CSF pressure was reduced to less than 10 cm H_2O (a level where we had demonstrated resolution of the transverse sinus narrowing, see above) the IIH persisted[30].

At about the same time we observed a patient with IIH who had developed a low-pressure headache after an LP. Our initial reaction was to suspect the original diagnosis of IIH was incorrect, how could a patient with markedly elevated pressure develop a low-pressure headache it did not seem to make sense. On review of the patient's medical record it was clear that she fulfilled the diagnostic criteria[34-37].

A low-pressure headache represents prolonged drainage of CSF resulting in a low pressure, usually less than 5 cm H_2O. Clinically the headache of IIH is distinct from that of low-pressure headache with the latter abolished by lying flat with the foot of the bed elevated, but the only way to differentiate with certainty between IIH and low-pressure headache is to measure the CSF opening pressure. We subsequently undertook a review of all cases of IIH seen at the Geelong hospital. One patient had developed a low-pressure headache after the insertion of a lumbo-peritoneal shunt that had to be removed. IIH resolved in this patient but recurred some years later. A second patient developed a low-pressure headache in the setting of a temporary lumbar drain with permanent resolution of IIH. There were 10 other patients who had complete resolution of IIH (average follow-up 3 years (range 3 mo-10 years) following the development of a low-pressure headache. In 2 patients low CSF pressure was confirmed by LP (5 and 7 cm H_2O). There was one patient in whom the IIH persisted and who was clinically suspected of developing a low-pressure headache; the low pressure was not confirmed by LP in this patient[29,30]. One young non obese female patient has subsequently relapsed.

One possible explanation for these observations is that a low-pressure headache represents prolonged drainage of CSF reducing the external pressure on the transverse sinuses, relieving the physiological stenosis of these sinuses and allowing the vicious cycle of raised pressure to normalise. If this interpretation is correct then a way to explore this concept is to undertake a study of patients with IIH using controlled lumbar drainage, a technique that has been employed to control medically refractory increased intracranial pressure[38]. The CSF may need to be drained at a faster rate than has been traditionally recommended and the duration of drainage is uncertain. This could be explored in a multicentre study where the rate of and the duration of CSF drainage could be varied with each centre learning from prior experience. After the period of drainage the CSF pressure could be measured after a period of clamping of the drain for a minimum of 2 h (enough time for the volume of CSF in the ventricles to be restored, *i.e.,* 25 mL with a production rate of 0.37 mL/min). If the CSF remains elevated then one could undertake a further period of drainage at a faster

rate and/or for a longer period, once again measuring the CSF pressure after clamping the drain. An online database could be established to share observations and hopefully establish the ideal rate and duration to drain the CSF.

CONCLUSION

This paper has explored the concept that IIH may represent a vicious cycle of elevated intracranial pressure, triggered by unknown factor(s) that could potentially be interrupted by prolonged drainage of CSF as seen with a post-LP induced low-pressure headache or by prolonged lumbar drainage without the necessity of inserting a permanent lumbo-peritoneal shunt or transverse sinus stenting. The lumbar drain would need to drain CSF at a faster rate than 0.37 mL per minute in order to reduce the CSF pressure to a level low enough for the increased interstitial fluid to diminish back to its normal state.

Until such an approach is confirmed patients with severe IIH particularly if vision is threatened should be managed along conventional lines.

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MINIREVIEWS

Involvement of leak K^+ channels in neurological disorders

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Abstract

TWIK-related acid-sensitive K^+ (TASK) channels give rise to leak K^+ currents which influence the resting membrane potential and input resistance. The wide expression of TASK1 and TASK3 channels in the central nervous system suggests that these channels are critically involved in neurological disorders. It has become apparent in the past decade that TASK channels play critical roles for the development of various neurological disorders. In this review, I describe evidence for their roles in ischemia, epilepsy, learning/memory/cognition and apoptosis.

Key words: Leak K^+ channel; TWIK-related acid-sensitive K^+ channel; Neurological disorder

Core tip: The leak K^+ conductance generated by TWIK-related acid-sensitive K^+ (TASK) channels is crucial for neuronal excitability. Because of the substantial expression of TASK channels in the brain, it is possible that these channels are responsible for numerous neurological disorders. However, little is known about the roles of TASK channels in the development of neurological disorders. In this review, I introduce the molecular basis of leak K^+ channels and describe the possible roles for TASK channels in several neurological disorders.

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INTRODUCTION

The neurological disorders are diseases of the brain, spinal cord, and nerves that make up the nervous system. There are a large number of neurological disorders such as epilepsy, Parkinson's disease and stroke. To date, many studies have been demonstrated that various ion channels expressed in the nervous system are involved in the development of neurological diseases[1,2]. The ion channels are classified into voltage-gated, ligand-gated, mechanosensitive and leak channels based on the control mechanism, while being classified into Na^+, K^+, Ca^{2+} and Cl^- channels based on the ion selectivity[3]. In recent years, the molecular basis of ion channels has been elucidated through the development of the molecular cell biology and genetic engineering method. However, much of the roles of ion channels in pathophysiological conditions including neurological

disorders remains unclear[4]. In this review, I will discuss the roles of leak K^+ channels in neurological disorders. In particular, I will focus on the TWIK-related acid-sensitive K^+ (TASK); TWIK, for tandem P domains in a weak inwardly rectifying K^+) channels (*e.g.,* TASK1 and TASK3) due to the high expressions in the central nervous system.

LEAK K^+ CHANNELS

Based on the structural features, K^+ channels are classified into three major families[5]. Members of the first family of K^+ channels include the voltage-gated K^+ channels (the delayed rectifier and transient voltage-dependent K^+ channels)[6] and Ca^{2+}-dependent K^+ channels[7] and form tetramers with each subunit containing six transmembrane domains and one pore domain. Members of the second family of K^+ channels include the inwardly-rectifying K^+ channels such as ATP-sensitive K^+ channels[8] and form tetramers with each subunit containing two transmembrane domains and one pore domain. Members of the third family of K^+ channels include the leak K^+ (two-pore-domain K^+) channels[5,9] and form dimers with each subunit containing four transmembrane domains and two pore domains. In excitable cells such as neurons, a negative membrane potential is critical for electrical signaling, and it has long been considered that this key mechanism is largely mediated by leak K^+ currents. However, the molecular basis for characterizing functional properties of leak K^+ currents remained unknown until recently. In the 1990s, the discovery of the *KCNK* gene family has been described whose members generate the hallmark properties of leak K^+ currents[9]. In mammalians, fifteen subunits have been identified and divided into six subfamilies (TWIK, TREK, TASK, TALK, THIK, and TRESK) on the basis of sequence similarity and functional resemblance[4,9]. The TWIK group includes the weakly inwardly rectifying channels (TWIK1, TWIK2, and the nonfunctional KCNK7); the THIK group includes halothane-inhibited THIK1 channel and related non-functional THIK2; the TREK group includes the arachidonic acid and mechanosensitive channels (TREK1, TREK2, and TRAAK); the TALK group includes the alkaline-activated channels (TASK2, TALK1, and TALK2/TASK4); the TASK group includes acid-sensitive channels (TASK1, TASK3, and the nonfunctional TASK5); the TRESK group includes Ca^{2+}-activated channels (TRESK1). Among fifteen subunits of leak K^+ channels described above, TASK1 and TASK3 are widely expressed in the central nervous system[10].

TASK CHANNELS

TASK channels are two-pore–domain channels that generate pH-sensitive K^+ currents with little time-dependence and weak rectification[5]. In heterologous expression systems, TASK5 was found to be inactive while TASK1 and TASK3 were able to form functional homomeric channels[9]. In addition, there is evidence that TASK1 and TASK3 might form functional heterodimers *in vitro* and *in vivo*[11,12]. The unitary conductance of TASK3 channel (approximately 28 pS) is about two times larger than that of TASK1 channel (approximately 14 pS)[13]. Although the macroscopic currents arising from these two channels are similar, the sensitivity to extracellular pH is different. The pK for TASK1 inhibition is approximately 7.4 while that for TASK3 is approximately 6.7[13]. TASK channels are inhibited by extracellular acidification, local anesthetics and G-protein-coupled receptors[5]. In contrast, TASK channels are activated by phospholipids and volatile anesthetics such as halothane and isoflurane[5].

INVOLVEMENT OF TASK CHANNELS IN NEUROLOGICAL DISORDERS

Ischemia

Neuronal damage caused by ischemic stroke is a major health care problem for persistent disability and death in clinical practice[14]. When ischemic state occurs, the transient membrane depolarization is induced in neurons. Consequently, the release of neurotransmitters such as glutamate, neuropeptide and Zn^{2+} is enhanced[15]. It is well known that the excessive glutamate causes neurotoxicity including neuronal dysfunction and degeneration. When the ischemic events continue to occur, cell death is induced[16]. On the other hand, mild hypoxia can induce neuroprotective signaling cascades that prevent neuronal death[17,18]. The activation of K^+ channels causes membrane hyperpolarization, which increases cell survival during cellular stress conditions. The decreased neuronal activity and the resultant lower metabolic demands could enhance neuronal survival under stress conditions. Thus, the protective effect of K^+ channels would reduce the development of ischemic stroke.

TASK1 and TASK3 channels are sensitive to acidic pH and hypoxic conditions. In addition, TASK3 homomeric channels are selectively suppressed by Zn^{2+}[19]. Considering that acidic pH and hypoxia are observed and the release of Zn^+ is enhanced during ischemic conditions, it is likely that TASK1 and TASK3 channels are involved in the development of ischemic stroke. Indeed, the roles of these channels in the ischemic stroke development have been revealed by pharmacological inhibitors and genetic knockout (KO) mice. In a study using a mouse model of cerebral ischemia, transient middle cerebral artery occlusion (MCAO), the infarct volume in TASK1 KO mice was significantly larger than that in its control mice while there was no significant difference in the infarct volume between TASK3 KO and its control mice[20]. The increased infarct volume could be mimicked by the TASK1 inhibitor anandamide[20]. Furthermore, in a study using a mouse model of permanent MCAO, the expression of TASK1 channel gene reduced the infarct volume, most likely

by a general influence on blood pressure[21]. These finding suggest TASK1 expressed in the brain decreases neuronal damage when stroke occurs.

Epilepsy

Epilepsy is a brain disorder that is characterized by the presence of spontaneous episodes of neuronal discharges[22]. Excessive and/or synchronous discharges in the brain cause the disruption of consciousness and disturbance of sensation and movement[22]. K^+ channels contribute to nearly all aspects of cellular electrical signaling and are important determinants of seizure susceptibility[23]. Therefore, K^+ channels have been considered as practical targets for anti-epileptic drug development.

In pathological conditions such as ischemia and epilepsy, it has been demonstrated that the extracellular pH was changed in the brain[24,25]. In the CA1 hippocampal areas, recurrent epileptiform activity caused biphasic pH shifts, consisting of an initial extracellular alkalinization followed by a slower acidification[25]. The authors indicated that the different extracellular pH shifts between CA1 and dentate gyrus might have caused the regional difference in seizure susceptibility between these two areas[25]. Because TASK channels are highly sensitive to changes in extracellular pH, several studies implicated the involvements of these channels in the generation of epilepsy. The changes in neuronal excitability within the hippocampus are one of the hallmarks of temporal lobe epilepsy[26]. Therefore, it is conceivable that TASK channels expressed in the hippocampus play essential roles in the generation of epilepsy. First, the role of TASK1 channels in epilepsy was investigated in the hippocampus of gerbils[27]. Between the hippocampi of young seizure-resistant (SR) and seizure-sensitive (SS) gerbils (1 to 2 mo old), there was no difference in the TASK1 and TASK2 immunoreactivites. In adult SS gerbil hippocampus, TASK1 immunoreactivity in astrocytes was higher compared to the adult SR gerbil hippocampus. After seizure events, TASK1 immunoreactivity was significantly downregulated in astrocytes of the SS gerbil hippocampus. Furthermore, several anti-epileptic drugs selectively reduced the TASK1 immunoreactivity in astrocytes of the SS gerbil hippocampus[27]. These findings indicated that upregulation of TASK1 channels in astrocytes may be responsible for the seizure activity of adult SS gerbils and that downregulation of TASK1 channels in astrocytes may suppress the seizure activity. In addition to TASK1 channels, the role of TASK2 channels in epilepsy was examined by using a rat model of experimental temporal lobe epilepsy[28]. Following status epilepticus, TASK2 expression in the CA1 pyramidal cell layer was downregulated, probably due to damage or loss of CA1 pyramidal cells. On the other hand, the TASK2 expression was significantly upregulated in the dentate granuler and CA3 pyramidal cell layers and endfeet of perivascular astrocytes[28]. These findings suggest that upregulation of TASK2 channels may make a contribution to adaptive responses by inducing hyperpolarization and reducing seizure activity.

Ion channels are essential for the regulation of excitability in the central nervous system[3]. It is believed that various inherited diseases associated with abnormal excitability of the affected neurons are caused as a result of mutations in ion channel encoding genes[2]. Several studies reported the discovery of epilepsy-related mutations in genes encoding TASK channel proteins. Childhood absence epilepsy is an idiopathic, generalized, nonconvulsive epilepsy that occurs in otherwise normal children. The *KCNK9* gene coding for the TASK3 channel is present on chromosome 8 in a locus that shows positive genetic linkage to the human absence epilepsy phenotype[29]. Furthermore, in the genetic absence epilepsy rats from Strasbourg (GAERS), an additional alanine residue in a polyalanine tract within the C-terminal intracellular domain was detected in the *KCNK* gene. For this reason, *TASK3* channels were regarded as a promising candidate gene for absence epilepsy. However, there were no significant differences in the physiological properties between the wild-type and mutant *TASK3* channels[30]. In addition, leak K^+ currents were almost similar between thalamocortical neuros in GAERS and nonepileptic animals[30]. These observations suggest that *TASK3* gene was not associated with absence epilepsy. On the other hand, a mutation analysis of the *TASK3* gene was performed in patients with children and juvenile absence epilepsy[31]. Only one silent polymorphism was detected in exon 2 of the TASK-3 coding region. However, since there was no relationship between the exon 2 polymorphism and absence epilepsy[31], the human TASK-3 appears not to be involved in the absence epilepsy.

Apoptosis

During brain development, the cell excitability is an important determinant for neuronal survival and proliferation[32]. K^+ channels are responsible for the resting membrane potential and action potential duration. Activation of K^+ channels results in membrane hyperpolarization, which significantly influences neuronal death or survival. It has been demonstated that activation of K^+ channels induced neuronal apoptotic cell death[33,34] whereas it protected neurons from ischemia[35] and glutamate-induced cell death[36]. Previous studies revealed that the expression of TASK channels may substantially affect cell viability in either direction[37]. It has been demonstrated that TASK3 channels are responsible for K^+-dependent apoptosis in cultured cerebellar granule neurons. Neuronal death was caused by apoptosis when cerebellar granule neurons were cultured *in vitro* in physiological K^+ concentration, but was prevented when they were cultured in high K^+ concentration. The cell death of granule neurons was also suppressed by pharmacological inhibition

of TASK3 channels with extracellular acidosis and ruthenium red. The cell death was in parallel with the expression level of TASK3 channels[37]. These results indicate a direct relationship between the activity of TASK3 channels and programmed cell death that is necessary for shaping the appropriate cerebellar structure. The authors have also shown that genetic transfection of TASK channel subunits into cultured hippocampal neurons induced apoptotic effect. On the other hand, viral overexpression of TASK3 in cultured hippocampal slices increased cell survival during cellular stress conditions such as an oxygen-glucose deprivation injury[38]. These results suggested that the activation of TASK3 channels can also be protective in neurons under cellular stress conditions.

Learning, memory and cognition

TASK1 and TASK3 channels are widely expressed in the central nervous system. Therefore, it is suggested that the deletion of TASK1 and/or TASK3 channels affects learning and memory. However, in TASK1 KO mice, the higher brain functions were almost similar to the wild-type mice[39]. For example, there were no appreciable differences in anxiety-related behavior and stress-induced hyperthermia between the wild-type and TASK1 KO mice, although the deletion of TASK1 enhanced the sensitivity to thermal nociceptive stimuli[39]. By contrast, TASK3 KO mice exhibited pronounced behavioral changes in relation to memory functions compared with the TASK1 KO mice[40]. In T-maze spontaneous alternation test, the performance in the TASK3 KO mice was poorer compared to the wild-type mice, indicating that working memory was impaired. In addition, during training for the Morris water-maze spatial memory task, the TASK3 KO mice were slower to find the hidden platform, suggesting the impairment of learning[40]. In TASK3 KO mice, the action potential generation and sustained repetitive firing to suprathreshold depolarization were impaired in the granule neurons[41]. Since long term synaptic changes induced by spike activity are believed to underlie learning and memory[42], it is possible that the reduced working memory is ascribed to the impaired spike activity caused by the deletion of TASK3.

CONCLUSION

TASK channels produce background K^+ currents that are time- and voltage- independent, and play crucial roles in setting the resting membrane potential and controlling the K^+ homeostasis. These channels are distributed abundantly in the central nervous system and involved in neurological disorders. Therefore, TASK channel subunits can serve as the molecular targets for treatment of neurological disorders. However, the roles of TASK channels in neurological disorders are just beginning to be investigated. Future studies on the TASK channels will be able to provide even more revealing insights into the neurological disorders.

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