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Carroll, Camille B.; Wyse, Richard K.H.

Published in:

Journal of Parkinson's Disease

DOI:

[10.3233/JPD-171203](https://doi.org/10.3233/JPD-171203)

Publication date:

2017

Link:

[Link to publication in PEARL](#)

Citation for published version (APA):

Carroll, C. B., & Wyse, R. K. H. (2017). Simvastatin as a Potential Disease-Modifying Therapy for Patients with Parkinson's Disease: Rationale for Clinical Trial, and Current Progress. *Journal of Parkinson's Disease*, 0(0). <https://doi.org/10.3233/JPD-171203>

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Review

Simvastatin as a Potential Disease-Modifying Therapy for Patients with Parkinson's Disease: Rationale for Clinical Trial, and Current Progress

Camille B. Carroll^a and Richard K.H. Wyse^{b,*}

^a*Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK*

^b*The Cure Parkinson's Trust, Marylebone, London, UK*

Accepted 7 October 2017

Abstract. Many now believe the holy grail for the next stage of therapeutic advance surrounds the development of disease-modifying approaches aimed at intercepting the year-on-year neurodegenerative decline experienced by most patients with Parkinson's disease (PD). Based on recommendations of an international committee of experts who are currently bringing multiple, potentially disease-modifying, PD therapeutics into long-term neuroprotective PD trials, a clinical trial involving 198 patients is underway to determine whether *Simvastatin* provides protection against chronic neurodegeneration. Statins are widely used to reduce cardiovascular risk, and act as competitive inhibitors of HMG-CoA reductase. It is also known that statins serve as ligands for PPAR α , a known arbiter for mitochondrial size and number. Statins possess multiple cholesterol-independent biochemical mechanisms of action, many of which offer neuroprotective potential (suppression of proinflammatory molecules & microglial activation, stimulation of endothelial nitric oxide synthase, inhibition of oxidative stress, attenuation of α -synuclein aggregation, modulation of adaptive immunity, and increased expression of neurotrophic factors). We describe the biochemical, physiological and pharmaceutical credentials that continue to underpin the rationale for taking *Simvastatin* into a disease-modifying trial in PD patients. While unrelated to the *Simvastatin* trial (because this conducted in patients who *already* have PD), we discuss conflicting epidemiological studies which variously suggest that statin use for cardiovascular prophylaxis may increase or decrease risk of developing PD. Finally, since so few disease-modifying PD trials have ever been launched (compared to those of symptomatic therapies), we discuss the rationale of the trial structure we have adopted, decisions made, and lessons learnt so far.

Keywords: Parkinson's disease, Simvastatin, disease modification, clinical trial

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative condition with age being the main risk factor for its development [1]. With longevity

having increased in most Western countries, a conservative estimation in 2007 predicted that the global number of PD patients will increase to approximately 10 million by 2030 [2]. By 2010, there were approximately 630,000 PD patients in the USA, a figure that was thought set to double by 2040 [3]. However, recent figures suggest these striking predictions may themselves be substantial underestimates since the incidence rates for PD now appear to be

*Correspondence to: Richard KH Wyse, Director of Research and Development, The Cure Parkinson's Trust, 120 Baker St, Marylebone, London W1U 6TU, UK. E-mail: richard@cureparkinsons.org.uk.

39 increasing each decade [4]. While these figures are
40 alarming in themselves, especially given the burden
41 to patients and to their families, these demographics
42 also demonstrate the massive impact on each
43 country's healthcare services that PD brings.

44 For example, the costs in the USA of managing
45 PD were estimated in 2013 at \$23 billion, which is
46 \$38,000 per patient per year [5], a figure to
47 which must be added the additional \$10,000 per
48 patient/family of indirect costs that their PD incurs
49 them. Furthermore, PD patients get progressively
50 more expensive to manage as their condition deteriorates
51 over time. Accordingly, increasing annual healthcare
52 costs per PD patient are associated with more advanced
53 stages of the disease, with greater burden resulting
54 from cognitive decline, increased non-motor symptoms
55 and development of balance impairment and falls. Therefore
56 there is a compelling need, shared by patients, families
57 and healthcare systems alike, to identify a cost-effective
58 approach to intercept disease progression, to slow, stop
59 or even reverse neurodegeneration in a rapidly expanding
60 global population of PD patients. It is projected that
61 if PD disease progression could be slowed by just
62 20% it would overall save approximately \$76,000 per
63 patient, rising to a saving of approximately \$440,000
64 per patient if PD progression could be stopped altogether
65 [5]. Both these scenarios would translate to far better
66 long-term quality of life for PD patients, as well as
67 saving billions of healthcare dollars every year by all
68 major Western countries. Currently, only symptomatic
69 treatments are available to PD patients since no
70 disease-modifying therapy has yet been demonstrated
71 to be effective in slowing PD progression, which
72 highlights what is currently a huge unmet need for
73 the identification of effective neuroprotective PD
74 therapeutics.

75 For this reason, the International PD Linked Clinical
76 Trials initiative was established in 2012 with the
77 specific aim of identifying disease-modifying
78 treatments for PD that would slow, stop or reverse
79 the neurodegenerative aspects of this condition. The
80 International PD Linked Clinical Trials is run by a
81 committee of 15 global PD experts who, under the
82 stewardship of the Cure Parkinson's Trust, are
83 tasked with selecting, and sending into appropriately-
84 designed clinical trials, compelling new and repurposed
85 therapeutics to evaluate their disease-modifying
86 potential in various different populations of patients
87 with PD. At their first ever committee meeting in
88 2012, 26 potential disease-modifying candidate drug
89 approaches for slowing

91 PD progression were evaluated. At that meeting,
92 several of these therapeutics were prioritized to
93 enter PD disease-modifying trials, and they have
94 since entered, or have now recently completed
95 (Bydureon), these clinical evaluations. On the basis
96 of compelling biochemical, physiological and pharmaceutical
97 arguments, coupled with a strong safety record, *Simvastatin*
98 was one of the drugs prioritized at that meeting [6].
99 Accordingly, funds were subsequently raised and this
100 *Simvastatin* clinical trial in PD patients was
101 commenced in September 2015 [7]. This *Simvastatin*
102 study is co-funded by the Cure Parkinson's Trust and
103 the JP Moulton Foundation. This on-going 2 year
104 trial involves 198 patients with mid-stage idiopathic
105 PD and is currently being carried out in movement
106 disorder units in 23 hospitals across the UK. Projected
107 completion of this trial is in early 2020.

108 The current paper discusses the original biochemical,
109 physiological and pharmaceutical rationale that led
110 the committee in 2012 to agree that this trial was
111 strongly merited to explore the disease-modifying
112 potential of *Simvastatin* for treating PD. It also
113 updates to October 2017 the rationale for conducting
114 this trial in terms of our current understanding of
115 the relevant mechanisms of action and biological
116 targets of *Simvastatin* that continues to maintain
117 our enthusiasm about the use of this therapeutic as a
118 disease-modifying approach for patients with PD.

119 This paper also strives to achieve a balanced view
120 of a range of conflicting epidemiological studies
121 surrounding the use of statins for cardiovascular
122 protection, and whether statin use for this purpose
123 may increase or decrease PD risk.

124 Finally, this paper describes details about our ongoing
125 *Simvastatin* trial and outlines the decisions made
126 about its design, as well as aspects about patient
127 selection, patient recruitment, the dose of *Simvastatin*
128 chosen, investigator site selection, rationale on how
129 the duration of the trial was chosen, and the choices
130 of which patient outcomes are being measured.

131 **WHY DOES SIMVASTATIN REPRESENT A** 132 **STRONG CANDIDATE TO BE A** 133 **DISEASE-MODIFYING THERAPEUTIC** 134 **FOR PATIENTS WITH PARKINSON'S** 135 **DISEASE?** 136

137 What is the biochemical, physiological & pharmaceutical
138 rationale for testing *Simvastatin* in PD patients
139 as a long-term disease-modifying therapy?

140 Although statins have been widely adopted in mil- 191
141 lions of patients worldwide as cholesterol lowering 192
142 drugs to reduce cardiovascular risk, a very wide 193
143 range of laboratory studies (described below) coa- 194
144 lesce to suggest that statins also modulate some of 195
145 the important biochemical processes involved with 196
146 driving neurodegenerative changes, and may there- 197
147 fore offer a beneficial long-term disease-modifying 198
148 therapeutic approach to reduce neurological decline 199
149 in PD patients. 200

150 Several laboratory studies have demonstrated mul- 201
151 tiple biochemical neuroprotective effects of statins 202
152 in models of PD; these will be reviewed and dis- 203
153 cussed below. *Simvastatin*, like all statins, is a specific 204
154 inhibitor of the rate-limiting enzyme in cholesterol 205
155 biosynthesis, and it is one of the most effective of the 206
156 statins in terms of crossing the blood-brain barrier, 207
157 while *Pravastatin* shows almost no penetration [8]. 208
158 In fact the permeability of different statins into the 209
159 brain directly relates to the level of their individual 210
160 lipophilicity [9, 10].

161 In addition to their original pharmaceutical use 211
162 in lowering cholesterol, statins display multiple 212
163 neuroprotective effects. For example, Selley [11] 213
164 reported that *Simvastatin* prevents methyl-4-phenyl- 214
165 1,2,3,6-tetrahydropyridine (MPTP)-induced striatal 215
166 dopamine depletion and protein tyrosine nitration 216
167 in mice. Ghosh et al. [12] then found, at a dose 217
168 of 1 mg/kg body weight/day (which is equivalent to 218
169 the FDA-approved dose in adults), that *Simvastatin* 219
170 enters the substantia nigra, inhibits the activation of 220
171 p21(ras), suppresses the activation of NF- κ B, atten- 221
172 uates the expression of proinflammatory molecules, 222
173 protects dopaminergic neurons, restores striatal fibers 223
174 and dopamine levels, and improves locomotor func- 224
175 tion in an acute MPTP model of PD. They concluded 225
176 by suggesting that statins are capable of slowing down 226
177 the progression of neuronal loss in the MPTP mouse 227
178 model. 228

179 In an excellent and extensive review, Roy and 229
180 Pahan in 2011 [13] outlined the evidence for five sep- 230
181 arate pathways, each thought to be of relevance in 231
182 PD neurodegenerative aetiopathogenesis, by which 232
183 *Simvastatin* may improve dopaminergic neuronal 233
184 survival :- 234

- 185 • suppression of proinflammatory molecules and 235
186 microglial activation 236
- 187 • stimulation of endothelial nitric oxide synthase 237
- 188 • inhibition of oxidative stress 238
- 189 • attenuation of α -synuclein aggregation 239
- 190 • modulation of adaptive immunity 240

201 One of the objectives of the current review is to 211
202 update these biochemical and pharmaceutical find- 212
203 ings to the present day to help give a perspective 213
204 on the rationale of why a clinical trial testing *Sim- 214*
205 *vastatin* as a potential disease-modifying therapeutic 215
206 for patients with PD is currently underway. Below is 216
207 our current interpretation (updated to October 2017) 217
208 of the multiple cholesterol-independent biochemical 218
209 mechanisms of action of *Simvastatin* as originally 219
210 cited by Roy and Pahan in 2011 [13] that we believe 220
211 specifically support the biochemical, physiological 221
212 and pharmaceutical reasons underpinning this inno- 222
213 vative clinical trial. We add to this 2011 list, the topic 223
214 of the stimulation of increased expression of neu- 224
215 rotrophic factors by statins which was not covered 225
216 by Roy & Pahan in 2011 but since then, in the con- 226
217 text of neurodegenerative diseases, has shown also 227
218 to be of considerable relevance to the other pleiotropic 228
219 effects of statins mentioned above. 229

230 *Suppression of proinflammatory molecules and* 231 *microglial activation*

232 In 2011, Roy & Pahan [13] collated evidence that 241
233 inflammation and oxidative stress represent impor- 242
234 tant components in nigrostriatal degeneration in PD 243
235 [14–20]. At that time it was already well established 244
236 that cytokines were central to the inflammatory pro- 245
237 cesses that accompany various forms of acute and 246
238 chronic brain injury, and many research laboratories 247
239 around the world had begun to focus with therapeutic 248
240 intent on PD. Ghosh et al. [19] also notably found 249
241 that NF- κ B was activated within the substantia 250
242 nigra pars compacta of PD patients and in MPTP- 251
243 intoxicated mice. Roy and Pahan [13] then discussed 252
244 how statins might be harnessed to reduce neuroin- 253
245 flammation in a Parkinsonian context. 254

255 At that time, the evidence for this potentially 256
257 important property of statins was that Pahan et al. 257
258 [21] had already shown *Lovastatin* inhibits NF- κ B, 258
259 iNos expression and the proinflammatory cytokines, 259
260 TNF- α , IL-1 β and IL-6 in lipopolysaccharide (LPS)- 260
261 stimulated rat primary astrocytes. Adding to earlier 261
262 work by Stanislaus et al. [22], Neuhaus et al. [23] 262
263 using in cells taken from multiple sclerosis patients 263
264 demonstrated that *Simvastatin* is more potent as 264
265 an effective immunomodulatory agent than either 265
266 *Lovastatin* and *Mevastatin*. 266

267 To add to this, Clarke et al. [24], building 267
268 on the fact that they knew statins generate pow- 268
269 erful anti-inflammatory effects in brain, reported 269
270 that *Atorvastatin* exerts these effects via IL-4, and 270

241 completely independent of its cholesterol-lowering
242 actions. These results were supported by other find-
243 ings [12, 25] which showed how p21(ras) inhibits the
244 expression of iNOS by inhibiting the activation of
245 NF-kappaB, while Pahan et al. [21, 26] demonstrated
246 how farnesylation can impact on these biochemi-
247 cal processes, and how the sphingomyelin-ceramide
248 signaling pathway is involved with stimulating the
249 expression of iNOS via LPS- or cytokine-mediated-
250 activation of NF-kappaB in astrocytes. The current
251 state of knowledge at that time on these aspects had
252 been well described and summarized by van der Most
253 et al. [27], after which Santiago et al. [28] then showed
254 that *Simvastatin* protected striatal dopaminergic ter-
255 minals against the neurotoxic damage caused by LPS,
256 but not in an MPP+ toxic model. Liu et al. [29] have
257 recently explored how the inflammatory responses in
258 microglia may be controlled in PD-related models
259 and postulating that Nur77 may be a modulator of
260 microglia-mediated dopaminergic neurotoxicity.

261 Building on earlier work which showed that statins
262 protect neurons in models of long-lasting status
263 epilepticus and seizures, Gouveia et al. [30] found
264 that *Lovastatin* protectively decreased mRNA expres-
265 sion levels of the proinflammatory cytokines, IL-1 β ,
266 IL-6, and TNF α in hippocampal neurons during
267 experimental status epilepticus. Using a mouse model
268 of Alzheimer's disease (AD), Kurata et al. [31] found
269 that, after 15–20 months of treatment, both *Atorvas-*
270 *tatin* and *Pitavastatin* were protective of senile plaque
271 formation, and that this protection was preceded by a
272 reduction of proinflammatory events including levels
273 both of activated microglia and TNF- α . This sup-
274 ported earlier work by Tong et al. [32] who had
275 found in amyloid precursor protein transgenic mice
276 that *Simvastatin* attenuated inflammation, oxidative
277 stress and reduced amyloid beta levels and the num-
278 ber of affected neurites. *Simvastatin* had also been
279 shown to protect against tissue injury in the context
280 of ischemia-reperfusion injury [33], and in a model
281 of cardiopulmonary bypass to protect against cere-
282 bral and systemic inflammation, neuronal loss and
283 memory impairment [34].

284 Using a 6-hydroxydopamine model of PD and
285 a 3 week administration of *Simvastatin*, Yan et al.
286 [35] presented evidence that NMDA receptor mod-
287 ulation, MMP9 (matrix metalloproteinase-9) and
288 TNF- α by *Simvastatin* could partially explain its
289 anti-inflammatory, neuroprotective effects. Using a
290 similar model of PD, Kumar et al. [36] then found in
291 a mixed behavioral and biochemical study that *Ator-*
292 *vastatin* (20 mg/kg) and *Simvastatin* (30 mg/kg) were

293 both protective of weight loss, locomotor activity, and
294 also decreased levels of the inflammatory cytokines,
295 TNF- α and IL-6 that are characteristic of this model.
296 They also found that these statins restored the deficits
297 in mitochondrial enzyme complex activity that are
298 also generated in their 6-hydroxydopamine model.

299 The notion that mitochondrial function might be
300 involved with the anti-inflammatory action of statins
301 was also highlighted by Esposito et al. [37] in a com-
302 pletely different model, that of spinal cord injury
303 (which also displays inflammation, neutrophil infil-
304 tration, nitrotyrosine formation, pro-inflammatory
305 cytokine expression, and nuclear factor (NF)- κ B
306 activation). They showed that PPAR- α (a major
307 arbiter of mitochondrial size and number) *contributes*
308 to the anti-inflammatory activity of *Simvastatin*.
309 Specifically, and describing their findings as the
310 demonstration of a new mechanism for the action of
311 statins, they showed that the anti-inflammatory prop-
312 erties of *Simvastatin* were substantially reduced in
313 a PPAR- α knockout model. Since, as well as over-
314 all mitochondrial function, the PPAR-alpha nuclear
315 receptor also regulates genes involved with inflam-
316 mation and oxidative stress, it is of particular
317 interest that they found PPAR- α mediates the anti-
318 inflammatory effects of *Simvastatin in vivo* models of
319 acute neuroinflammation. This built on their earlier
320 observation [38] that *Simvastatin* similarly worked
321 in synergy with PPAR- α to protect cellular damage
322 caused by systemic inflammation in a model of mul-
323 tiple organ failure. A recent report by Zhou et al.
324 [39] expands Esposito's findings in that they showed
325 *Simvastatin* is both neuroprotective and inhibits
326 secondary inflammatory damage by markedly down-
327 regulating the expression of the proteins (NF)- κ B,
328 TLR4 and IL-1 β .

329 Xu et al. [40] studied how *Simvastatin* affects
330 6-hydroxydopamine-lesioned PC12 through regula-
331 tion of PI3K/AKT/caspase 3 and by modulating
332 inflammatory mediators, and how it might be used
333 therapeutically to treat patients with PD. In a cel-
334 lular RNA study involving 6-OHDA administration,
335 Yan et al. [41] explored the involvement of N-methyl-
336 D-aspartic acid receptor 1 (NMDAR1) finding that
337 *Simvastatin* inhibits the expression of NMDAR1,
338 and of the cytokines, TNF- α , IL-1 β , and IL-6, in
339 a manner just as potent as using siRNA for the
340 receptor. In a retinal cell model, Zhang et al. [42]
341 reported that that *Simvastatin* inhibits apoptosis fol-
342 lowing IR-induced retinal injury by inhibition of
343 the TNF- α /NF- κ B pathway. With a PD therapeu-
344 tic perspective in mind, Zhang's findings should be

345 seen in the context that Malu Tansey's group had
346 previously described [43] how the TNF- α /NF- κ B
347 pathway mediates chronic inflammation which, in
348 turn may generate a reduction in Parkin levels, and
349 thereby increasing the vulnerability for degeneration
350 of the nigrostriatal pathway. They argued that chronic
351 inflammation offers a clear biochemical mechanism
352 which can promote the development of PD. Huang
353 et al. [44] recently showed in multiple models that
354 Simvastatin ameliorated memory deficits in patients
355 with Alzheimer's disease as well as in laboratory
356 models of AD, and that it achieved this through
357 reduction of mRNA expression of inflammatory
358 cytokines and mediators as well as by improv-
359 ing neuronal survival, supporting earlier work by
360 Wang et al. [45].

361 In summary, by directly inhibiting key inflamma-
362 tory processes, *Simvastatin* may therefore represent
363 a therapeutically beneficial disease modifying agent
364 with considerable potential to reduce the rate of PD
365 progression.

366 *Stimulation of endothelial nitric oxide synthase*

367 Roy & Pahan [13] also collated robust evidence
368 [14-15, 17, 21, 24-25] in 2011 which supported the
369 view that the upregulation of endothelial nitric oxide
370 synthase (eNOS) is generated by statins via suppres-
371 sion of mevalonate and concomitant activation of the
372 PI-3 kinase-Akt pathway. This built on Flint Beal's
373 supposition [46] that modulating eNOS might offer
374 a valuable neuroprotective therapeutic approach for
375 the treatment of PD. Statins inhibit iNOS expression,
376 while in contrast, they stimulate eNOS-derived nitric
377 oxide production, and this property appears biochemi-
378 cally unrelated to their ability to reduce cholesterol
379 [47]. Statin-induced upregulation of eNOS can be
380 reversed by geranylgeranyl pyrophosphate (but not
381 by farnesyl pyrophosphate) which intimates [13]
382 that Rac/Rho (rather than Ras) may be involved
383 in the regulation of eNOS. Fulton et al. [48] and
384 Skaletz-Rorowski et al. [49] demonstrated that Akt
385 phosphorylates eNOS, while mevalonate inhibits
386 phosphatidylinositol-3 kinase and thereby reduces
387 Akt activation. As statins lower mevalonate levels
388 (via inhibition of HMG-CoA reductase) it therefore
389 seems likely that reduction of mevalonate may trigger
390 increased eNOS production, and thereby increasing
391 NO levels. Atorvastatin has been shown [50, 51]
392 to promote NOS-derived nitric oxide production by
393 reducing expression of caveolin-1, and the therapeu-
394 tic implications of these HMG-CoA reductase effects

395 of statins are still being actively clarified in cardio-
396 vascular medicine [52, 53].

397 A recent review by Saeedi Saravi et al. [54] focuses
398 more specifically on the potential relevance of the
399 mevalonate pathway to the potential therapeutic ben-
400 efit that statins may offer in protecting against long
401 term neurodegeneration in PD patients. Bezaud's
402 group [55] now consider downstream modulation
403 of the sterol regulatory element-binding protein 1
404 (SREBP-1) pathway to be important in inducing
405 phenotypic changes in dopaminergic cells, includ-
406 ing increases in cell growth, synaptic connections
407 and protein expression. They have recently presented
408 additional data on this that supports a potential pro-
409 tective role of statins in PD [56]. Since SREBP-1 (and
410 SREBP-2) regulates promoter activity of PCSK9 [57]
411 there is therefore a clear link, with therapeutic impli-
412 cations, between SREBP-1 and PCSK9, and it was
413 recently shown that *Simvastatin* increases PCSK9
414 expression [58, 59] which may be therapeutically
415 relevant [60-63].

416 Sun et al. [64] showed in a cardiovascular context
417 that eNOS is a direct target of miR-155. Inflam-
418 matory cytokines such as TNF- α increase miR-155
419 expression and inhibition of miR-155 reverses TNF-
420 α -induced downregulation of eNOS expression.
421 They found that *Simvastatin* decreased TNF- α -
422 induced upregulation of miR-155 and ameliorated
423 the effects of tumor necrosis factor- α on eNOS
424 via the mevalonate-geranylgeranyl-pyrophosphate-
425 RhoA signaling pathway.

426 Pierucci et al. [65] reviewed in 2011 the promise
427 and opportunities of harnessing the NOS system to
428 treat PD, essentially building on the work by Hoang
429 et al. [66] who assessed the aspects and extent of the
430 nitrate damage, including in nuclear and mitochon-
431 drial DNA, that is caused in an MPTP model of PD,
432 and in a NOS knockout model, and from which they
433 concluded DNA damage may contribute to the over-
434 all neurodegenerative process in PD. Peter Jenner's
435 group [67] found evidence of a major role for i-NOS-
436 mediated nitrate stress in microglia in their MPP+
437 model of PD, which they concluded had important
438 implications for developing neuroprotective strate-
439 gies for PD, an argument which was further supported
440 by Tripathy et al. [68], and also recently reviewed by
441 Jiménez-Jiménez et al. [69] from the perspective of
442 studies both in PD patients, and in various PD models.

443 Li et al. [70] reported in 2015 how *Simvastatin*
444 is therapeutically beneficial following LPS-induced
445 experimental lung injury, showing it had a protec-
446 tive effect by alleviating lung injury via decreasing

447 iNOS levels. This ties in with the earlier findings
448 by Pahan et al. [21] who, as described above, had
449 already demonstrated that *Lovastatin* inhibits NF- κ B,
450 iNOS expression and the proinflammatory cytokines,
451 TNF- α , IL-1 β and IL-6 in LPS-stimulated rat primary
452 astrocytes.

453 Therefore, as well as its beneficial effects through
454 suppression of proinflammatory molecules and
455 reduction of microglial activation (as outlined in the
456 previous section), *Simvastatin* also appears to offer
457 substantial long-term disease-modifying benefits for
458 PD patients on the basis of decreasing microglia
459 iNOS levels and reducing chronic nitrative stress.

460 Along with the continued research into how NOS
461 may contribute to the neurodegenerative process in
462 PD, and may thus offer a therapeutic opportunity,
463 such as using *Simvastatin*, to delay PD progression,
464 a parallel line of research has explored how NOS
465 might be modulated for therapeutic benefit in treat-
466 ing a widespread clinical complication experienced
467 by many PD patients on long-term dopaminergic
468 support, that of L-DOPA-induced dyskinesias. How
469 NOS inhibitors might be employed in the treatment
470 of dyskinesias has been explored in experimental
471 studies using various PD models [71–74], and is
472 clearly showing promise for clinical translation for
473 the treatment of dyskinesias in PD patients. The
474 basis for this [75, 76] is that when inhibitors of the
475 MAPK signaling cascade impede the inappropriate
476 dyskinesia-inducing response of striatal neurons this
477 offers considerable evidence that MAPK inhibitors
478 may offer therapeutic efficacy in reducing incidence
479 and/or severity of dyskinesias experienced by PD
480 patients.

481 The isoprenylation of Ras is inhibited by statins
482 which underpins their ability to curb the stimulation
483 of ERK 1/2 MAP kinases, and Schuster et al. [77]
484 found that *Lovastatin* reduces the number and sever-
485 ity of dyskinesias in their 6-OHDA model of PD. In
486 particular, Tison et al. [78] found that *Simvastatin* was
487 indeed effective in reducing dyskinesias in a monkey
488 model of PD, but only at high doses that would be
489 incompatible with their long-term administration in
490 man, and which were 3-6 times higher than is being
491 used in the current clinical trial of *Simvastatin* in PD
492 patients (see below).

493 *Inhibition of oxidative stress*

494 Roy & Pahan [13] reviewed the evidence for
495 the involvement of statins in inhibiting the pro-
496 cess by which oxidative stress contributes to

497 neurodegeneration in PD, particularly focusing on
498 the roles of nicotinamide adenosine dinucleotide and
499 Rac, collating evidence that NADPH oxidase is vital
500 in terms of attrition of dopaminergic neurons. In fact
501 it was already known that nigral NADPH oxidase
502 is upregulated in MPTP mice, but that, conversely,
503 this toxin had no effect on dopaminergic neurons
504 in gp91phox (–/–) mice [79, 80]. Building on the
505 review by van der Most et al. [27], Roy & Pahan
506 [13] provided evidence that the inhibition by statins
507 of the geranylgeranylation of Rac leads to reduced
508 NADPH oxidase-mediated generation of superoxide,
509 which they interpreted as evidence statins may atten-
510 uate oxidative stress by diminishing the production of
511 reactive oxygen species both in the substantial nigra
512 of MPTP mice, and in PD patients via this biochem-
513 ical process.

514 Since then, much research has focused on the
515 role of Nrf2 (nuclear factor erythroid 2-related fac-
516 tor 2) in oxidative stress [81, 82], and how, in several
517 therapeutic areas, including PSP and PD [83], age-
518 related macular degeneration [84], oncology [85, 86],
519 cardiovascular disease [87, 88], arterial calcification
520 [89], spinal cord injury [90] and radiation dermati-
521 tis [91], this emerging biochemical insight might
522 be manipulated to therapeutic advantage. Nrf2 is
523 a cytoprotective master regulator of the transcrip-
524 tional response to oxidative stress; it has a rapid
525 turnover, and its role in neurodegenerative diseases
526 has been well described by Gan and Johnson [92],
527 and its diversity of actions and control with respect
528 to mitochondrial function were recently well reviewed
529 by Holmstrom et al. [93], and also by Dinkova-
530 Kostova et al. [94]. When reactive oxidative species
531 are at low levels, nuclear Nrf2 is suppressed by the
532 inhibitory protein, KEAP1, which sequesters Nrf2 in
533 the cytoplasm to prepare it for proteasomal degrada-
534 tion [95, 96], and which maintains Nrf2 at a relatively
535 low steady state level. However, increasing levels of
536 reactive oxidative species influence KEAP1 in a way
537 that progressively impairs its ability to target Nrf2 for
538 degradation. A link between Nrf2, MAPT expression
539 and the risk of PD has recently been postulated by
540 Wang et al. [97], and may possibly offer a mechanis-
541 tic glimpse of why tau/MAPT repeatedly appears in
542 large-scale GWAS studies of PD patients [98, 99] yet
543 its role in the generalized risk of developing PD, and
544 its specific role in neuroinflammation with regards to
545 PD, are both poorly understood [100].

546 Several agents (particularly Nrf2 activators), which
547 act on these biochemical pathways (by upregu-
548 lating antioxidant, anti-inflammatory, mitochondrial

549 biosynthetic, apoptotic mediator and cytoprotective
550 genes) have promising potential for the long-term
551 protection from neurodegeneration in PD patients.
552 These include monomethylfumarate [101], dimethyl-
553 fumarate [102], gliptins [103] and the triterpenoid,
554 RTA-408 [85], each of which have already been prior-
555 itized by the International PD Linked Clinical Trials
556 committee to enter clinical trials in PD patients to
557 determine their disease-modifying potential. As a
558 practical therapeutic approach in neurology, much
559 of the new understanding of the protective poten-
560 tial of activating Nrf2 resides in these emerging
561 publications and it is being rapidly translated into
562 disease-modifying agendas in PD, as well as in other
563 therapeutic areas. Urate probably also acts via the
564 Nrf2 antioxidant response pathway [104] and is cur-
565 rently being tested (using oral inosine) in a Phase
566 III trial in 270 PD patients to assess its disease-
567 modifying potential over a treatment duration of 2
568 years [105]. To add to all the other biochemical
569 actions of statins outlined in this review we can add
570 another LCT-prioritized drug, *Simvastatin*, to this
571 important list of Nrf2 activators that may all have
572 the potential to be used clinically to slow neurode-
573 generation in PD patients. In 2014 Abdanipour et al.
574 [106], studying PGC-1 α and Nrf2 expression on cell
575 survival and apoptosis demonstrated that *Lovastatin*
576 protects bone marrow stromal cell-derived neural
577 stem cells against oxidative stress-induced cell death,
578 and suggested it as a candidate for the treatment of
579 neurological diseases that involve oxidative stress.
580 Since then, several papers have added further sup-
581 port to the view that statins act as Nrf2 activators. Wu
582 et al. [107] recently reported that *Atorvastatin* reduces
583 damage in liver injury when exposed to inflammatory
584 stress, citing loss of the adaptive antioxidant response
585 mediated by Nrf2 as the basis for the biochemical
586 mechanism involved. *Simvastatin* was found by Jang
587 et al. [108] to induce heme oxygenase-1 via direct
588 activation of Nrf2 in human colon cancer cell lines.
589 Ferraro et al. [109] studied the effects of *Simvastatin*
590 in both lung inflammation and in a human neuroblas-
591 toma cell line and concluded that *Simvastatin* may
592 provide neuroprotection against neurotoxicity via
593 Nrf2 independently of its ability to inhibit cholesterol
594 synthesis. Furthermore, Yeh et al. [110] demonstrated
595 that the well known effect of statins to protect against
596 atrial fibrillation was generated by the activation of
597 Akt/Nrf2/heme oxygenase-1 signaling.

598 Hsieh et al. [111] was the first to show that iron
599 production from Heme oxygenase-1 activity may
600 play an important role in the increased apoptosis

601 in response to glucose deprivation in neuronal cells
602 pretreated with *Simvastatin* which acted by inducing
603 of Heme oxygenase-1, a process which was medi-
604 ated by Nrf2. They found in neuronal cells that the
605 iron chelator, desferrioxamine, blocked apoptosis,
606 which suggested that iron production from Heme
607 oxygenase-1 activity might drive increased apoptosis
608 in situations of glucose deprivation in neuronal cells
609 that had been pretreated with *Simvastatin*. Two PD
610 trials also prioritized by the international PD Linked
611 Clinical Trials committee in 2012 are underway to test
612 iron chelator therapy as a potential disease-modifying
613 treatment for patients with PD. One trial involves 338
614 early-stage PD patients who are not currently taking
615 antiparkinsonian medication (disease duration less
616 than 18 months) and who are taking the iron chela-
617 tor, Deferiprone [112], and the second dose-finding
618 trial [113], also using Deferiprone, is comprised of
619 140 PD patients who have been diagnosed with PD
620 within the last 3 years and who are currently taking
621 antiparkinsonian medication.

622 *Attenuation of α -synuclein aggregation*

623 In their 2011 review of the potential for using
624 statins to treat PD, Roy and Pahan [13] summarized
625 the knowledge at that time relating to how alpha-
626 synuclein impacts on dopaminergic toxicity and cell
627 loss, motor deficits, the synthesis of cholesterol, and
628 the deposition of alpha-synuclein-rich Lewy bod-
629 ies in the substantia nigra. They concluded that,
630 since statins suppress the release of proinflammatory
631 molecules from activated glial cells (see above), it
632 is likely they should also subdue malformed alpha-
633 synuclein-mediated glial cell activation in a manner
634 that is completely independent of cholesterol. As with
635 all the other sections in this review, much has moved
636 on over the past 6 years. A current view, held by many
637 (but not in 2011) is that malformed alpha-synuclein is
638 capable of cell-to-cell transmission and that this may
639 underpin the development of PD throughout the body,
640 but particularly involving spread from the enteric
641 nerves, and/or olfactory bulb, to the substantia nigra,
642 raphe, locus coeruleus, the cortex and several other
643 important anatomical sites which each contribute in
644 their own way to the range of PD symptoms we see
645 clinically [114–118].

646 Roy and Pahan [13] reflected on how *Lovas-*
647 *tatin*, *Simvastatin* and *Pravastatin* each generate
648 large reductions in alpha-synuclein accumulation
649 both in a transfected neuronal cell line, and in
650 primary human neurons [119], and that *oxidized*

651 cholesterol even promotes increased alpha-synuclein
652 aggregation [120]. This observation has recently been
653 somewhat supported by Eriksson et al. [121] who
654 interpreted their findings in a neuroblastoma cell line
655 exposed to MPP⁺ to reason that high cholesterol in
656 PD stimulates the accumulation of alpha-synuclein.

657 Once *Lovastatin* was also shown [122] to reduce
658 alpha-synuclein accumulation and aggregation in
659 transgenic models, it was logical to contemplate that,
660 since statins lower cholesterol levels, then they may
661 therefore directly reduce the aggregation of alpha-
662 synuclein in PD patients. Koob et al. concluded
663 that, while it was known as early as 2006 [123]
664 that, once mutated, alpha-synuclein causes a much
665 stronger glial cell inflammatory response, but that
666 since statins reduce the expression of these proinflam-
667 matory molecules they may well be found beneficial
668 as a long-term treatment for patients with PD. Given
669 the knowledge available at that time, Roy and Pahan
670 [13] therefore posed the logical question; do statins
671 suppress mutated alpha-synuclein-mediated glial cell
672 activation in a manner that is completely independ-
673 ent of cholesterol? Several papers, mostly published
674 since then, have gone some way to answering that
675 question [24, 124–131] – the widely-held consensus
676 answer is definitely yes, although there is still slightly
677 less clarity on the mechanistic details than we might
678 have wished for.

679 *Modulation of adaptive immunity*

680 Statins have been repurposed into several diseases
681 where innate and adaptive immunity and endothelial
682 damage play an important role [132]. To date, statins
683 have been specifically tested and used in atheroscle-
684 rosis [133], multiple sclerosis [134, 135], rheumatoid
685 arthritis [136], Behcet's disease [137], and Kawasaki
686 disease [138, 139] in many cases with very promis-
687 ing results. It was pointed out in the review by Roy
688 & Pahan [13] that effector T cells may exacerbate
689 disease progression (which can be demonstrated in
690 post mortem PD brains), while regulatory T cells
691 (Tregs) tend to occupy a protective role. It has been
692 found that T-cell responses in an MPTP model of
693 PD add to the rate of neurodegeneration [140–142]
694 while conversely, Tregs have been shown to be protec-
695 tive in an MPTP model of PD [143], and the reasons
696 behind this duality have previously been discussed
697 by Mosley et al. [144] and, since Tregs can be mod-
698 ulated *in vivo*, this gives strong support to the use
699 of an immunomodulatory approach to treat PD. In
700 2010, Reynolds et al. [145] demonstrated that natural

701 Tregs reversed the T cell nigrostriatal degeneration
702 caused by malformed alpha-synuclein, proposing that
703 this observation forms a sound rationale for future
704 PD immunization strategies. This approach has been
705 reviewed and expanded upon by several with consid-
706 erable clarity and insight [124, 130, 146, 147], and
707 most recently by Gendelman and Mosley [148] who
708 discussed approaching this topic in therapeutic terms
709 by postulating simultaneously to seek enhancing the
710 suppressive function of Tregs, while downregulating
711 proinflammatory cytokine production. They balanced
712 and tempered this by recognizing that immune system
713 activation is also necessary in order to clear debris
714 to help sustain and restore damaged neurons. They
715 offered 'mounting and strong evidence' that immune
716 transformation can affect the pathogenesis of neu-
717 rodegenerative diseases, and that modulation of the
718 inflammatory response, while restoring a homeostatic
719 immune system via immunopharmacological strate-
720 gies, may lead to new therapeutic opportunities for
721 PD and other neurodegenerative disorders.

722 Acting as a cytokine and neuropeptide which
723 impacts on immune responses, Vasoactive Intesti-
724 nal Peptide (VIP) induces Tregs. The neuroprotective
725 capability of Tregs is mediated through TH17, and It
726 has been suggested that shifting the balance between
727 effector and regulatory T cell activity by adaptive
728 immune regulation of glial homeostasis could be used
729 to attenuate neurotoxic inflammatory events [149].
730 By peptide modifications similar to those for GLP-
731 1 agonists that have given them greater potency and
732 much longer metabolically stable half-life in blood
733 than the native hormone, Olsen et al. [150] developed
734 an analogue of VIP and showed that to be an effective
735 immunomodulatory agent in an MPTP model of PD.
736 They concluded by stating they had provided "strong
737 evidence" that VIP receptor agonism has the potential
738 to slow the pathogenesis of PD through modulation
739 of the inflammatory response. This builds on the ear-
740 lier observation by Brachmachari and Pahan [151]
741 who, and citing *Foxp3* as a master regulator in Treg
742 formation and function, discovered that *Simvastatin*
743 upregulates *Foxp3* by inhibiting nitric oxide produc-
744 tion, going on to suggest that Treg enrichment by
745 *Simvastatin* may help to protect dopaminergic neu-
746 rons in the substantia nigra.

747 *Increased expression of neurotrophic factors*

748 This potential biochemical effect of statins was not
749 covered in the earlier review by Roy & Pahan [13].
750 Hernandez-Romero et al. [152], as well as demon-

751 strating the potency of *Simvastatin* in markedly
752 reducing inflammatory responses in LPS-induced PD
753 rats, including interleukin-1, TGF- α and iNOS (as
754 have several other groups, as described above), also
755 found that *Simvastatin* stimulated the activation of the
756 neurotrophic factor, BDNF. This suggests there may
757 be a profoundly neurogenic aspect to the mechanism
758 of action of *Simvastatin* in dopaminergic neurons.
759 This was followed up by Wu et al. [153] who showed
760 that *Simvastatin* increases the hippocampal expres-
761 sion of BDNF and VEGF in a model of brain injury.

762 They concluded that the neurorestorative effect of
763 *Simvastatin* they observed was probably be medi-
764 ated via the Akt-mediated signaling pathway, which
765 thereby upregulated expression of growth factors,
766 thus stimulating via neurogenesis the restoration of
767 cognitive function they observed with *Simvastatin*.
768 They employed a similar dose to that used in our
769 current clinical trial of *Simvastatin* in PD patients
770 (see below). It was then reported [154] in a model
771 of spinal cord injury that *Simvastatin* generated sig-
772 nificantly improved locomotor recovery, and this
773 improvement was ascribed to the higher levels of
774 expression of BDNF and GDNF which observed
775 in this study after administration of *Simvastatin*.
776 This contention was further supported when it was
777 reported [155] that both *Simvastatin* and *Atorvastatin*
778 increased the expression of BDNF, VEGF and NGF,
779 as well as activation of the Akt-mediated signaling
780 pathway, in an experimental model of intracerebral
781 hemorrhage. Furthermore, it was shown [156] that
782 *Simvastatin* modulates the profile of the release of
783 cytokines and trophic factors from microglia, (partic-
784 ularly interleukin-1 β , TNF- α , and BDNF) through a
785 mechanism that is cholesterol-dependent, and which
786 went some way to explain previously confusing con-
787 tradictions in laboratory results. Rana et al. [157]
788 then reported that *Simvastatin* increased expression
789 of BDNF exon-IIC transcripts in stressed mice. Wang
790 et al. [158] then reported that, in A β 25-35-mice,
791 *Simvastatin* is protective of neurogenesis through
792 reduction of farnesyl pyrophosphate level which
793 then generates α 7nAChR-cascading PI3K-Akt and
794 increased levels of BDNF. Next, Gao et al. [159]
795 demonstrated that *Simvastatin* significantly increases
796 the levels both of BDNF and GDNF in a model of
797 spinal cord injury, and then went on to show that
798 *Simvastatin* also reduces neuronal apoptosis while
799 promoting locomotor recovery in this model [160]. It
800 was recently shown [161] that *Simvastatin* promoted
801 the neurogenesis and migration of neural stem cells
802 with a mode of action involving the ROCK/CGTase

803 pathway. *Simvastatin* has also recently been demon-
804 strated to improve peripheral nerve regeneration and
805 functional recovery in an experimental model of sci-
806 atic damage that involves elevation of levels of GDNF
807 and several other growth factors [162]. Earlier this
808 year, it was reported [163] that *Atorvastatin* increased
809 serum BDNF levels and improved functional recov-
810 ery (modified Rankin and Barthel scales) in patients
811 following atherothrombotic stroke.

812 It had previously highlighted [20] that the
813 Nurr1/CoREST pathway in microglia and astrocytes
814 protects dopaminergic neurons from inflammatory
815 damage, and this is thought to be particularly relevant
816 here because Nurr1 activity is known to be closely
817 related to GDNF activity [164]. Wang et al. [158] also
818 demonstrated that *Simvastatin* induces autophagy by
819 inhibiting the mTOR signaling pathway. In 2015, Roy
820 et al. [165] then took a step forward to help tie the
821 various threads together in reporting that statins serve
822 as ligands for PPAR α and ascribed the neurotrophic
823 action of statins to be via the PPAR α -CREB path-
824 way. Until then there had been no receptor protein
825 identified for statins (they exert their *lipid-lowering*
826 actions quite differently, more structurally, as com-
827 petitive inhibitors of HMG-CoA reductase).

828 Finally, and here focusing on PD, unlike most of
829 the other neurological models described in this sec-
830 tion from which we are definitely able to draw useful
831 parallels, Castro et al. [166] reported on how *Ator-*
832 *vastatin* in an intranasal PD rat model caused in a
833 significant increase in striatal and hippocampal lev-
834 els of nerve growth factor, adding that their findings
835 ‘extend the notion of the neuroprotective potential
836 of *Atorvastatin* and suggest that it may represent a
837 new therapeutic tool for the management of motor
838 and non-motor symptoms of PD’, while in 2016,
839 Tan et al. [167] showed in an LPS model of PD
840 that *Simvastatin* restored the expression of BDNF, as
841 well as replicating earlier findings by many groups
842 that it reduces oxidative stress and improves nigral
843 function.

844 EPIDEMIOLOGICAL STUDIES ON THE 845 USE OF STATINS AND THE RISK OF PD

846 The purpose of this section is not intended as a
847 critical appraisal of epidemiological research in this
848 area, nor to generate data synthesis (in fact others
849 have previously attempted to do this - see below),
850 but rather to provide a catalogue, and a context, of
851 published studies.

Valid interpretation of published studies has been consistently confounded by the core reason why statins are taken, i.e., to reduce high levels of cholesterol, which in turn means there is inevitably a high correlation between the two explanatory variables, statin use and blood cholesterol levels. Partly because of this confounding inter-relationship, there is currently no clarity about whether statin use is protective of an individual developing PD, has no effect, or makes it more likely that an individual may develop the disease.

Most would agree that the hypothetical risk of a healthy individual acquiring PD through taking a particular medication, represents a very different scenario to using that same medication to treat the disease once it has already developed. Nevertheless, it is appropriate to discuss here, and bring a balance to, the various studies that have either linked the taking of statins to protecting healthy individuals against developing PD, or the converse.

We re-emphasize this ongoing epidemiological debate is actually of questionable relevance to patients who *already* have PD but it is appropriate in terms of our on-going trial of Simvastatin to use this opportunity to give a balanced scientific review of the viewpoints, the available evidence, and to highlight strengths and weaknesses in published papers in this area of research.

First, it is important to make the point that, since the initial isolation of statins from microorganisms in the 1970s, there has been a huge growth in their specific use in primary and secondary prevention of various forms of cardiovascular disease. In 2016, the US Preventative Services Task Force advised the use of statins for people between 40 and 75 years old who carry at least one risk factor for heart disease, and who have more than a 10% risk of heart disease [168]. Similarly, the UK National Institute for Health and Clinical Excellence has endorsed the use of statins in those with an estimated 10% risk of developing cardiovascular disease over the next decade [169]. The nature, interactions and pharmacokinetic relationships between cholesterol, apolipoproteins and statins were well described from a neurological perspective in a Cochrane review [170, 171] as a part of an original, then updated, analysis to consider the possible use of statins in the context of dementia prevention or treatment. They found 'insufficient evidence to recommend statins for the treatment of dementia'. Many PD patients develop cognitive impairment, but while none of those in that meta-analysis were PD patients, a recent paper

by Deck et al. [172] found that PD patients taking statins performed better on tests of global cognition, semantic fluency and phonemic fluency. Furthermore, although it is known that statins increase HDL and apolipoprotein A1 levels [173, 174], and that lower apolipoprotein A1 levels are associated with later stages of PD progression, Deck did not find that baseline apolipoprotein A1 levels correlated with any baseline neuropsychological measures.

Turning now to the question of whether the use of statins may positively or negatively influence the risk of developing PD, in 2006 and citing that epidemiologic investigations had revealed an association between low LDL-C levels and the risk of PD, with several studies previously having suggested a role of lipid and cholesterol metabolism in the pathogenesis of PD, de Lau et al. [175], studying >6000 patients, felt there might well be a role involving lipids in the pathogenesis of PD, and suggested that this provided support for the notion of an important role of oxidative stress in the pathogenesis of the disease.

An extensive review of patients in the Veterans Affairs healthcare system then found *Simvastatin* (but not *Atorvastatin* or *Lovastatin*) use was associated with a strong reduction in incidence of dementia and PD [176]. Wahner et al. [177] then found that all statins are inversely associated with PD (except for *Pravastatin*). They observed a higher frequency of statin use among controls versus PD cases. The strongest protective association between statin use and PD was observed in long-term (>5 yr) statin users. Huang et al. [178] then reported the results of a small epidemiological study of 124 PD patients and 110 controls which inferred that low LDL-C may be associated with a higher occurrence of PD, and that statin use for prophylactic cardiovascular protection may lower PD occurrence. What Huang did not report is whether their patients had low LDL levels prior to their diagnosis of PD, nor whether their LDL levels decreased after this diagnosis. Therefore, since statins are effective at lowering LDL cholesterol levels, it may well be that their study design intrinsically confused cause with effect. What is more is that this research was vastly underpowered in the sense that fewer than 20 of the 124 PD patients in this study were actually taking statins so the results cannot be viewed as reliable. Becker et al then reported in a case-control analysis involving 3637 PD patients and 3637 controls that the long-term use of statins or fibrates was not associated with a substantially altered relative risk of developing PD [179].

956 The same year, a study of approximately 50,000
957 Finnish citizens, with their baseline serum total
958 cholesterol stratified into five groups, reported that
959 those individuals with the highest levels of chole-
960 sterol were almost 90% more likely to develop PD
961 than those with the lowest levels of cholesterol [180],
962 concluding that, in subjects under 55 years of age,
963 our ‘large prospective study suggests that high total
964 cholesterol at baseline is associated with an increased
965 risk of Parkinson’s disease’.

966 A retrospective study involving a cohort of 419 PD
967 patients, showed that in PD patients who received
968 either a statin or a fibrate, their mean age of disease
969 onset was delayed by nearly 9 years when com-
970 pared with PD patients who were not taking any
971 lipid-lowering treatment [181]. They also found the
972 increase in the levodopa-equivalent daily dose over
973 2 years was significantly smaller in the group tak-
974 ing a statin (+24 mg) than in the matched control
975 group (+212 mg) ($p=0.004$), whereas the UPDRS
976 motor score progression was similar. Their conclu-
977 sion was that lipid-lowering drugs may have a disease
978 modifying effect.

979 The 2011 DATATOP study [182] then provided
980 evidence that higher total serum cholesterol con-
981 centrations may be associated with a modest slower
982 clinical progression of PD. The same team at Harvard,
983 using 12 years of patient follow-up, and following
984 644 documented incident cases of PD, then reported
985 [183] that regular use of statins was associated with
986 a modest reduction in PD risk. They suggested that
987 “the possibility that some statins may reduce PD risk
988 deserves further consideration”.

989 The following year Undela et al. [184] conducted
990 a robust meta-analysis of published healthy subjects
991 and found, across five separate case-control studies
992 ($n=43,526$) and three cohort studies ($n=1.4$ million),
993 that statin use reduced an individual’s risk of getting
994 PD by 23% ($p=0.005$), but no such effect was found
995 for *long-term* statin use. They substantiated their find-
996 ings by conducting further sensitivity analysis and
997 concluded that their results ‘suggest a decreased rel-
998 ative risk of PD in statin users as identified by a
999 combined meta-analysis of eight observational stud-
1000 ies’. Friedman et al. [185] then reported their findings
1001 following 94,308 (initially) non-statin users who did
1002 not have PD. By the end of their study, there had
1003 been 1035 incident cases of PD. Furthermore, 29,714
1004 participants (31.5%) had started using statins for a
1005 minimum of 6 months during the study period. This
1006 statin use was associated with a significant decrease in
1007 the incidence of PD ($p=0.001$), while no association

1008 was found between baseline LDL-C levels and PD
1009 risk. Friedman felt their results provided evidence
1010 relating to a lower incidence of PD among statin
1011 users.

1012 This contention was further supported by a report
1013 from Taiwan [186] following for several years 43,810
1014 individuals who had started taking a statin, and
1015 backed up by an excellent commentary by Tan and
1016 Tan, [187]. It was found that continuation of tak-
1017 ing lipophilic statins was associated with a decreased
1018 incidence of PD, whereas taking hydrophilic statins
1019 appeared not to generate this benefit.

1020 Then, Huang et al. [188] reported results of a
1021 prospective study involving 15,291 individuals with-
1022 out PD and mostly who were not statin users at study
1023 commencement. Over approximately a decade statin
1024 usage had increased to 11.2% of the study popula-
1025 tion, and there were 56 incident cases of PD. As
1026 in their 2011 paper [182] they reported that higher
1027 total cholesterol was associated with a lower risk of
1028 developing PD, even after adjustment for statin use.
1029 Unlike their earlier studies they calculated that statin
1030 use may be associated with a higher risk of acquiring
1031 PD which added further uncertainty to this topic, and
1032 also attracted considerable journalistic interest.

1033 To try to gain some clarity on whether statins were
1034 protective or not in terms of initially developing PD,
1035 Bai et al. [189] and Sheng et al. [190] both pub-
1036 lished extensive meta analyses of relevant results to
1037 date. Bai’s meta-analysis involved 3,513,209 indi-
1038 viduals and included 21,011 incident cases of PD.
1039 Sheng’s meta-analysis involved 2,787,249 individ-
1040 uals. The results of both studies were in complete
1041 agreement that statin use was associated with a much
1042 lower risk of PD ($p=0.001$) and that sensitivity anal-
1043 yses confirmed the robustness of these results. They
1044 found that statin use was less protective of PD in
1045 North America than in other geographies, which is
1046 something that may account for some of the con-
1047 jecture and mixed results that had been published
1048 previously. Furthermore, and adding to this complex-
1049 ity in terms of confounding interpretation of statin
1050 use in the context of PD epidemiology, Clark et al.
1051 [191] found that the frequency of treatment success
1052 in dyslipidemia management was significantly lower
1053 in African American patients in the USA than in
1054 non-Hispanic white patients, while Yood et al [192]
1055 found that African American patients initiating statin
1056 therapy are less likely to achieve LDL goals, even
1057 after controlling for adherence differences and other
1058 factors, and suggested that this group may require
1059 different pharmacologic management.

Huang's group then reported in 2016 [193] that higher levels of LDL-cholesterol were associated with improved executive set shifting and fine motor scores in PD patients, but not in healthy controls. This small study (64 PD cases) did not contain many statin users to be meaningful on interpreting this aspect but interestingly, they hypothesized from their results that there may possibly be an association between cholesterol and cognition that is nigrostriatal-based while very fairly pointing out that they could not currently ascertain whether this relationship was causative, reverse-causative or a parallel process.

Earlier this year Huang's group [194] used a large US claims database of people who had chosen to enroll in private healthcare insurance schemes in order to interrogate this team's earlier 2015 contention [188] that statin use may be linked to a higher risk of PD. This time they included 21,599 individuals who, during the period of their analysis generated 2322 incident cases of PD who, for statistical analysis, were then matched with an identical number of healthy controls. Consistent with several earlier studies, they found that higher levels of cholesterol was associated with a lower risk of PD. They also reported that the use of statins (especially lipophilic statins) was associated with higher risk of PD.

Rozani et al. [195] recently published a 232,877 population-based cohort study of new statin users in whom 2,550 developed PD during a mean follow-up of 7.6 years. The study was unusual in that throughout this time the researchers comprehensively made multiple repeated measurements both of statin exposure and LDL-levels. Contrary to Huang's findings [188, 194], and agreeing with the results of many other studies [176–179, 181, 183–187, 189, 190] they found no association between annual statin adherence and PD risk regardless of age, or type of statin taken.

Understandably, those taking statins, or consider taking a statin, to reduce their cardiovascular risk want to know whether this choice would also bring them an increased likelihood of developing PD? This is a very different question to whether a statin might represent a disease-modifying therapeutic for use in patients who have *already* developed PD, and our ongoing 2 year clinical trial involving approximately 200 PD patients seeks specifically to determine whether *Simvastatin* slows PD progression.

As can be seen above, there have been several epidemiological studies investigating whether there may be an association, protective or otherwise, of statin use in relation to subsequent development of PD. These have recently been evaluated in a systematic

review and meta-analysis by Bykov et al. [196] that helpfully discusses the methodological strengths and weaknesses of each these earlier epidemiological studies. It is fair to say that the methodologies utilized in the epidemiological papers cited above all have limitations. Association does not imply causation. Bykov found that overall there seems to be a protective effect of statins against development of PD, but that if cholesterol levels are adjusted for, then this protective effect disappears, and there is no association one way or the other with PD development. The authors also describe some of the limitations of epidemiological study design, including the 'healthy user' and 'immortal time' biases among others [197].

A brief description of the key findings from many of the various types of epidemiological studies that have attempted in recent years to determine whether the use of statins is positively or negatively associated with PD risk are summarized in Table 1.

With regard to Huang's most recent publication suggesting that *Simvastatin* may facilitate development of PD [194], there are some key limitations which merit highlighting: large sectors of the population were not represented in the database that was analyzed (particularly the elderly, i.e., over 65 s, were excluded); and only those with private health insurance were included. It is possible that some patients in this study were misdiagnosed because the clinical details of the participants, and diagnostic confirmation, was not available to the researchers. The authors found that PD was more likely to be diagnosed within the first year or so of starting *Simvastatin*. However, it is well acknowledged that PD starts at least 5 years, if not 10 years before diagnosis; it has also been demonstrated by others that healthcare contacts increase in the year or two prior to diagnosis, which could be what led to their being prescribed a statin. It is well known that vascular risk factors increase risk of dementia, and it would not be unreasonable to suppose that the same might hold true for other neurodegenerative diseases. It is likely that most people taking a statin were started on it because of their vascular risk, and that this might have been the contributory factor that was identified in the study. Indeed, a UK cohort study has demonstrated worse PD severity with increased cardiovascular risk, and underutilization of statins in the PD population [198]. The association of cholesterol and statins as risk factors for PD development has recently been discussed in a *Lancet Neurology* review by Ascherio & Schwarzschild [104], which concluded that any possible association remains uncertain.

Table 1

Key findings from various epidemiological studies that have attempted to determine whether the use of statins is positively or negatively associated with PD risk

Reference and Research team	Study Type & Size	Results	Statistics and additional information
Wolozin et al. [176]	Retrospective analysis of VA database of 4.5 million subjects, which included 700,000 SV users	Protective. SV 'strongly protective' of PD risk	SV use reduced the Hazard Ratio (0.51) $p < 0.001$
Huang et al. [178]	Case control study involving 124 PD cases and 112 controls	Protective. Use of cholesterol-lowering drugs (primarily statins) in this study group was associated with a lower occurrence of PD	Odds Ratio = 0.36–0.41
Wahner et al. [177]	312 PD cases versus 343 controls. Population-based case control study of incident PD	Protective. 3 of 5 different statins were associated with approximately a 55% reduction in PD risk	Statistically significant Risk Reduction for SV, AV, LV, but not for PV. Odds Ratios ($p < 0.01$) were 0.38, 0.39 and 0.27, respectively
Becker et al. [179]	Case-control observational analysis involving 3,637 PD patients (378 of whom had or were taking statins), and 3,637 controls	No difference found between PD patients and controls	Odds Ratio = 1.06
Mutez et al. [181]	Retrospective analysis of a cohort of 419 PD patients	Protective. Mean age of onset of PD delayed 9 years by statin use	Levodopa-equivalent daily dose also reduced in the group taking a statin
Gao et al. [183]	Prospective study of 129,066 healthy subjects, 644 of whom developed PD over 12 years of follow-up	Protective. Regular use of statins was associated with a modest reduction in PD risk	Relative Risk was 0.74, $p < 0.05$, and for subjects under 60 years, Relative Risk was 0.31, $p = 0.02$
Undela et al. [184]	Meta-analysis, combining 5 case control studies and 3 cohort studies which studied 1.4 million subjects including 15,102 PD cases	Protective. Statin use over a 2–14 year follow-up reduced risk of PD by 23%	Relative Risk = 0.77, $p = 0.005$
Friedman et al. [185]	94,308 subjects without PD or statin use at baseline. Over 7 years, 1035 developed PD, and 29,714 took statins for at least 6 months	Protective. Statin use up to 2.5 years of follow-up in 15,394 patients was associated with a significantly reduced risk of PD	Odds Ratio for reduced risk of PD = 0.69, $p < 0.001$ No association noted between baseline LDL-C levels and PD risk
Lee et al. [186]	Study followed 43,810 statin users without PD, 1,985 of whom went on to develop PD	Protective. Use of lipophilic statins, either SV or AV, each reduced the incidence of emergent PD	SV and AV significantly reduced the Hazard Ratio (0.23–0.42) for PD risk depending on age and gender. The incidence rate for PD was 1.68 and 3.52 per 1,000,000 person-days for lipophilic and hydrophilic statins, respectively
Huang X et al. [188]	Prospective study of 15,792 subjects over 9 years, 106 of whom developed PD while another 187 subjects may have developed PD but this could not be clinically confirmed	Disadvantageous. Statin use was associated with a higher risk for PD when adjusted for cholesterol levels	Odds Ratio = 2.30, $p < 0.05$ In addition, higher total cholesterol was associated with lower risk for PD after adjustment for statin use
Liu et al. [194]	Retrospective case control analysis involving 2,322 probable incident PD cases and 2,322 controls. Same research team as 188	Disadvantageous. Statin usage was significantly associated with PD risk	Strongest associations with PD risk was for lipophilic statins (Odds Ratio = 1.58, $p < 0.0001$), whereas for hydrophilic statins (Odds Ratio = 1.19, $p = 0.25$)

(Continued)

Table 1
(Continued)

Reference and Research team	Study Type & Size	Results	Statistics and additional information
Rozani et al. [195]	Population-based cohort of statin initiators. 232,877 new statin users were followed for 7+ years, and in whom there were 2,550 emergent cases of PD	Statin adherence over time did not affect PD risk	All-risk estimates were close to unity (except for a slightly reduced PD risk: Hazard Ratio = 0.77 among women aged 40–45 with LDL-C level 160 mg/dl at baseline) Results unaffected by whether statins were lipophilic or hydrophilic
Bai et al. [189]	Meta-analysis, combining 5 case control studies and 6 cohort studies which studied 3.5 million subjects (1.1 million statin users), and including 21,011 incident cases of PD	Protective. Statin use was associated with a reduced risk of PD	Because of the low incidence of PD, the authors felt distinctions among RR, HR, and OR could be ignored, allowing combined case-control and cohort studies, and calculated the summary Relative Risks and 95% CIs. Relative Risk for reduced PD risk was 0.81, $p = 0.002$
Bykov et al. [196]	Meta-analysis, of ten eligible epidemiological studies	Protective, but only in the six studies analyzed that did not adjust for cholesterol. Protective effect of statins against PD risk, Relative Risk = 0.75 95%CI: 0.60 to 0.92	No protective effect was observed among the four studies that adjusted for either cholesterol or hyperlipidemia Relative Risk = 0.91; 95%CI 0.68 to 1.22
Sheng et al. [190]	Meta-analysis, of 11 studies (2,787,249 subjects) including 5 case-control and 6 cohort studies	Protective. Use of statins was associated with a significant reduction in risk of developing PD	Adjusted Relative Risk = 0.74, 95% CI 0.62 to 0.90, $P < 0.001$

Results, and outcomes measures used, are as described by the respective authors. SV, Simvastatin; AV, Atorvastatin; LV, Lovastatin; PV, Pravastatin.

In conclusion, we reiterate, whether PD risk is increased or decreased by taking a statin to lower cardiovascular risk (and a clear future demonstration of the reality of this would be valuable and welcome), that the testing of a statin to treat PD neurodegeneration in patients who already have established PD is a completely separate and unrelated question. It therefore remains highly reasonable to pursue Simvastatin in a randomized clinical trial to test its disease-modifying potential in a population of PD patients (see biochemical/pharmaceutical rationale described earlier). In this Simvastatin trial [7] we are measuring PD severity and so will pick up whether or not the rate of PD progression is affected by Simvastatin, hopefully in a positive direction as that is the point of the trial. We are carefully monitoring for adverse events and at the end of the study in 2020 we will finally be able to evaluate the unblinded data.

DESCRIPTION OF CURRENT LCT CLINICAL TRIAL OF SIMVASTATIN

No drug has yet been shown to slow or reverse the neurodegenerative process of PD. All currently

licensed therapies act as symptom-relieving agents but have a limited lifespan of effectiveness because of continued neuronal loss. The purpose of *this* study, as mandated by the International PD Linked Clinical Trials Committee [6], is to determine whether *Simvastatin*, a widely used cholesterol-lowering drug (statin) with an excellent safety profile, is capable of reducing the rate of neurodegenerative decline in patients with PD. Details of this clinical trial are described on the US clinical trials website [7]: <https://clinicaltrials.gov/show/NCT02787590>.

Briefly, after considerable discussion about how best to configure an appropriate long-term *disease-modifying* trial in PD patients (rather than a symptomatic study), a randomized, double-blind, placebo-controlled, two year study was chosen, to be conducted in idiopathic PD patients who, at study commencement, had been characterized as Modified Hoehn and Yahr stage ≤ 3.0 in the ON medication state. It was made a requirement for entry into the trial that they were on dopaminergic treatment with wearing-off phenomenon.

Participants are randomly allocated to one of two treatment groups. In one group, participants are given capsules of *Simvastatin* to take orally (by mouth) for 24 months.

The other group receives placebo capsules to take orally for 24 months. At the start of the study, when they receive their medication, participants complete a number of questionnaires and motor (movement) tests (a walking test and a finger tapping test). Participants in both groups also attend a further 6 clinic visits after 1, 6, 12, 18 and 24 and 26 months, where they are asked about their health and any medication they are taking, as well as repeating the questionnaires and motor tests. For 4 of the clinic visits, having omitted their usual PD medication that day, the participants are asked to attend in the 'OFF medication' state so that the researchers can get a true picture of their disease without it being masked by their normal medication.

The *Simvastatin* trial is a 198 patient, 23 Centre, Phase II, randomized, placebo-controlled, double-blinded study, officially titled '*Simvastatin* as a Neuroprotective Treatment for Parkinson's Disease: a Double-blind, Randomised, Placebo Controlled Futility Study in Patients of Moderate Severity'. The primary outcome measure is Change in MDS-UPDRS part III (OFF) score, and the duration of treatment is 24 Months. The Secondary Outcome Measures include MDS-UPDRS total score in the practically defined ON state, MDS-UPDRS part II subscale score in the practically defined ON state, Timed motor tests - finger tapping and timed walk test, Timed Motor Tests include evaluating the number of hand taps that an individual can perform within 30 seconds and a timed walk test. In addition, the following rating scales are used to evaluate the study participants: Montgomery and Asberg Depression Rating Scale (MADRS), The Addenbrooke's Cognitive Assessment-III (ACE-III), Non-Motor Symptom assessment scale (NMSS), Parkinson's disease Questionnaire (PDQ-39), Changes in PD medication as measured by levodopa-equivalent dose (LED), Cholesterol levels (total, HDL, total/HDL ratio), King's PD pain scale (KPPS), EuroQoL 5D-5L health status questionnaire (EQ-5D-5L), Safety and tolerability of trial medication by adverse events (AEs) review, and Incidence of diabetes mellitus.

Active comparator: A one month low dose phase of 40 mg oral *Simvastatin* daily is followed by a 23-month high dose phase of 80 mg oral *Simvastatin* daily and a final two month phase off trial medication.

Matched Placebo Comparator: A one month low dose phase of 40 mg matched placebo daily is followed by a 23 month high dose phase of 80 mg matched placebo daily and a final two month phase off trial medication.

Outline of choices made about the Simvastatin trial

Patient population

We elected to recruit patients in mid-stage disease, H&Y < or = 3 in the ON state, but who had developed motor fluctuations. The reason for this was two-fold. First, we felt that the trial findings would be of relevance to people living with PD today. Second, the presence of wearing off reduces the degree of heterogeneity in the study population, particularly for ensuring, as much as possible, consistency in the 'practically-defined off' state used for the primary outcome measure.

Study sites

We selected a multi-center design as it would not be possible to recruit the required number of participants from a single center. Within the UK we have an established Clinical Research Network that facilitates study delivery within centers experienced in PD clinical study delivery. The multi-center nature of the study does introduce issues relating to quality control, particularly with regard to rater experience and training. We therefore carried out feasibility assessments with sites expressing interest, stipulating the study requirements in terms of rater uniformity for the study duration, the need for an independent rater (separate from the rest of study delivery), rater experience and training (kindly provided by the MDS for this study). In addition, the study co-ordinating center has robust data management and site monitoring processes to ensure quality data collection across all sites.

Dose of Simvastatin chosen

We chose to use a dose of 80 mg of *Simvastatin* for this study, as this was the dose shown to have an excellent protective effect in the MS STAT trial involving treating Multiple Sclerosis patients [135, 199]. There are safety concerns regarding the use of high dose *Simvastatin*, particularly in the elderly. The overall risk of statin-induced myopathy is approximately 1%. We have introduced robust guidance and safety procedures into the protocol to mitigate this risk.

Choice of selected duration of clinical trial

Study duration was chosen as 24 months to maximize the potential for differences in progression between placebo and active treatment group. It is known that the placebo effect in PD studies is large and sustained. In addition, with a relatively small sample size and a clinically heterogeneous condition, it is important to allow sufficient time for measurable disease progression across the study population.

Choice of primary patient outcome

Choice of primary outcome measure was the OFF state MDS-UPDRS part III as this is the most likely to correlate with underlying disease severity and therefore be indicative of disease progression. This does not reflect clinical meaningfulness for patients whose OFF state UPDRS score will be improved by symptomatic medication; however, demonstrating clinical utility is not the purpose of this preliminary study. If this study suggests that *Simvastatin* does have potential as a neuroprotective agent, then a further Phase III study can evaluate impact on clinically meaningful outcomes, such as patient reported measures, quality of life measures, and cognitive decline.

Other design aspects

In order to distinguish a protective effect from a potential symptomatic effect a washout design was chosen with a 2-month washout period after the end of the 24-month treatment period. The half-life of *Simvastatin* is less than 5 hours, and so this period provides sufficient time for drug elimination.

DISCUSSION

The international PD linked clinical trials committee, based on a range of evidence compiled into a detailed dossier, and followed by extensive committee discussions, agreed in 2012 to prioritize *Simvastatin* to enter a trial in PD patients to assess its potential as a disease-modifying therapy [6]. Clinical trials of potential neuroprotective agents in PD are difficult to design. This is partially because of the variability in disease phenotype and rate of progression, and also, the potential confounding factor of a symptomatic response. In addition, there is no reliable biomarker for disease progression. The International PD Linked Clinical Trial committee is tasked to analyze potential new target therapies for PD and for which the biochemical evidence indicates the likelihood that they may have benefit to slow, halt

or reverse disease progression in patients with PD. This large global committee of PD experts, many of whom have extensive experience in PD trials and their design, is coordinated by The Cure Parkinson's Trust. The detailed biochemical, physiological, and pharmaceutical evidence available to the committee in 2012 which led them to choose to prioritize *Simvastatin* to enter a disease-modifying clinical trial is summarized in the first section of the current paper, with very substantial updating to October 2017. It is interesting to observe that the rationale, then in 2012, for taking *Simvastatin* into a PD trial to assess its disease-modifying potential (in fact, there are several separate mechanistic rationales as outlined above) has continued to strengthen over those 5 years on all biochemical and physiological fronts. Another recent review by Saeedi Saravi et al. [200] also summarizes, but more generally across several neurodegenerative diseases, the biochemical and pharmaceutical mechanisms of action of how statins may be beneficial in the management of these conditions. In their discussion of the treatment of multiple sclerosis they explore research into how immunomodulatory and anti-inflammatory properties of statins may helpfully unite for therapeutic benefit [201–203] and this may also be of direct relevance to the long-term management of PD. This is especially poignant since *Simvastatin* has already shown encouraging long-term clinical results in patients with multiple sclerosis [135, 199, 204], and a major Phase III study involving almost 1200 patients being given high dose *Simvastatin* (80 mg daily) will commence in the coming months. We have long established strong lines of communication between those involved with the multiple sclerosis (MS-STAT) and *Simvastatin* (PD STAT) trials.

Taking the example, also conceptually relevant to PD, of the costs of some of the newer multiple sclerosis (patented) therapeutics that are pursuing disease-modification objectives, several of these currently exceed \$75,000 per patient per year [205]. By contrast, the annual cost per patient of 80 mg *Simvastatin* (now unpatented) is \$37 per year [206], although that is not to say that the cost effectiveness of those high value therapies render them financially unusable [207–209], as this can vary across patient subgroups which in turn means that direct therapeutic, or even financial, comparisons with *Simvastatin* cannot always readily be made. However, there may be situations in the future where low cost unpatented drugs like *Simvastatin* may look a very attractive therapeutic alternative for healthcare providers, while

the patient perspective can be somewhat different and must also be taken in to account [210] because health economic algorithms currently used often miss substantial additional social value.

The first, biochemical, section of this paper demonstrates that *Simvastatin* acts on a number of separate, distinct intracellular processes, each of which appear of relevance to the long-term management of PD. These remain highly active research topics and we eagerly anticipate developments into this growing insight. When a repurposed therapeutic such as *Simvastatin*, has multiple pleiotropic effects, all or any of which may be clinically beneficial, there sometimes comes a point when one may just acknowledge we cannot identify a clear therapeutic target (because there are so many positively-orientated candidate modes of action), and go ahead and test it in the clinic. To quote John Overington from BenevolentAI, 'although the concept of a single drug target is a natural one for researchers in the field, there are substantial operational difficulties in consistently mapping this target concept to specific genes and gene products' [211]. Clearly, having a strong and extensive safety record has helped us move *Simvastatin* into a long-term trial in PD patients to explore its disease-modifying potential. We anticipate our current *Simvastatin* trial in PD patients will finish in 2020.

ACKNOWLEDGMENTS

This work is supported by the Cure Parkinson's Trust and the J P Moulton Charitable Foundation.

CONFLICTS OF INTEREST

RW is the Director of Research and Development at the Cure Parkinson's Trust which is an international grant-giving charity focused on delivering fundamentally innovative disease-modifying treatments that slow, stop or reverse Parkinson's disease. He declares no conflicts of interest relevant to this publication.

CC is the chief investigator of PD STAT, a clinical trial exploring *Simvastatin* as a neuroprotective treatment for patients with Parkinson's disease. She has no other conflicts of interest relevant to this publication.

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