

SUPPLEMENTARY MATERIALS

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SUPPLEMENTARY FIGURE 2 Doi plot showing major asymmetry between all studies

SUPPLEMENTARY TABLE 1 Objective adherence rates for injectable DMTs

Author, year	DMT(s)	Sample size	Adherenc e measure	Adherence: Cut-off score (≥ 80 unless specified)				Adherence:	
				<8 months	12 months	24 months	>36 months	<8 months	12 months
Agashiva la, 2013 ⁴¹	IFN β -1b, IFN β -1a, GA	<i>n</i> =1,64 3	MPR, PDC					MPR: (≥ 80): 77.4%;	MPR: <i>M</i> =0.87, <i>SD</i> =0.16;
								PDC (≥ 80): 49.9%	PDC: <i>M</i> =0.68, <i>SD</i> =0.31
Bayas, 2015 ³⁷	IFN β -1a s.c.	<i>N</i> =912 (safety populat ion)	Electronic Autoinject or					Autoinject or (>95): 84.3%;	Autoinject or: <i>M</i> =0.97, <i>SD</i> =0.73
								Autoinject or (<75): 2.1%	
Bruce, 2010 ¹⁴	GA, IFN β -1a, IFN β -1b	<i>N</i> =67	MEMS					MEMS (≥ 80): 82.0%	

Cerghet, GA, $n=111$ MPR
 2010⁴⁴ IFN β -1a,
 IFN β -1b
 Cohan, IFN β -1a, $n=531$ MPR,
 2018⁴⁵ IFN β -1b (no PDC
 switch)
 ; $n=117$
 (switch
)

MPR:
 $M=0.78,$
 $SD=0.27$
Stable
users:
MPR:
 $M=0.92,$
 $SD=NR$
Switchers:
MPR:
 $M=0.78,$
 $SD=NR$
Stable
users:
PDC:
 $M=0.86,$
 $SD=NR$
Switchers:
PDC:
 $M=0.74,$
 $SD=NR$

Cohen, GA, $n=2,41$ MPR
 2015⁴⁶ IFN β -1a, 0
 IFN β -1b

MPR
(≥ 80):
 79.0%;

Defer, 2018 ⁴⁹ IFN β -1a s.c. *n*=253 Electronic Autoinject or

Deftereos, 2018 IFN β -1a s.c. *n*=62 Electronic Autoinject or

Degli Esposti, 2017 ⁴⁰ IFN β -1a, IFN β -1b, GA *N*=1,698

Devonshire, 2016 ⁵¹ IFN β -1a s.c. *n*=158 Electronic Autoinject or

Duquette, 2019 ⁹ IFN β -1a, IFN β -1b, GA *n*=4,607 (6-month); *n*=2,711 (12-month);

MPR
(≥ 80):
65.0%

Autoinjector (≥ 80):
82.9%

MPR: 53.0% **MPR:** 47.0% **MPR:** 35.0%

Autoinjector:
M=0.98,
SD=0.57

Autoinjector:
M=0.89,
SD=0.20

		<i>n</i> =2,71				
		2 (24-				
		month)				
Evans,	IFNβ-1a,	<i>N</i> =4,74	MPR,		MPR:	PDC
2017 ⁵⁴ ;	IFNβ-1b,	6	PDC		(≥80):	(≥80):
2016 ⁵⁵	GA	(2017);			75.1%.	42.4%
		<i>N</i> =4,83			PDC:	
		0			(≥80):	
		(2016)			76.4%	
Fernández,	IFNβ-1a	<i>N</i> =258	Electronic			Autoinjector (≥80):
2016 ⁵⁷	s.c.		Autoinjector			86.8%
			or			
Gerber,	IFNβ-1a,	<i>n</i> =2,70	MPR		MPR	
2017 ⁵⁹	IFNβ-1b,	9			(≥80):	
	GA				62.3%	
Hansen,	IFNβ-1a,	<i>N</i> =50,0	MPR			MPR
2015 ¹⁰	IFNβ-1b,	57				(≥80):
	GA					39.9%
Jones,	GA	<i>N</i> =5,82	MPR			MPR
2013 ⁶⁰		5				(≥80):
						74.3%

Kleinman , 2010 ⁶¹	IFN β -1a, IFN β -1b, GA	<i>N</i> =358	MPR			MPR: <i>M</i> =0.74; <i>SD</i> =0.28
Kleiter, 2017 ⁶²	IFN β -1b s.c.	<i>n</i> =143	Electronic Autoinject or	Autoinject tor (≥ 80): 80.5%		
Kozma, 2014 ⁶³	IFN β -1a, IFN β -1b, GA	<i>N</i> =4,60 6	PDC		PDC (≥ 80): 67.3%	
Krol, 2017 ⁶⁴	IFN β -1a s.c.	<i>N</i> =1,68 2	Electronic Autoinject or			Autoinject tor (≥ 80): 82.9%
Lafata, 2008 ¹⁹	GA, IFN β -1a, IFN β -1b	<i>N</i> =224	MPR			

Lugaresi, 2012 ⁶⁶	IFN β -1a s.c.	<i>n</i> =119	Electronic Autoinject or	Autoinject tor (≥ 80): 88.2%		
McKay, 2017 ⁶⁷	IFN β -1a, IFN β -1b, GA	<i>N</i> =135	MPR		MPR (≥ 80): 57.0%	
Melesse, 2017 ³⁵	IFN β -1a, IFN β -1b, GA	<i>N</i> =721	PDC	PDC (≥ 80): 80.0%;		PDC (≥ 80): 86.0%
Moccia, 2015 ⁶⁹	IFN β -1a s.c	<i>N</i> =114	Electronic Autoinject or			Autoinject tor (≥ 80): 95.6%
Munsell, 2017 ⁷⁰	IFN β -1a, IFN β -1b, GA	<i>n</i> =7,20 7	MPR	MPR (≥ 80): 54.1%		MPR: <i>M</i> =0.69, <i>SD</i> =0.30
Oleen- Burkey, 2011 ⁷¹	GA	<i>N</i> =839	MPR		MPR (≥ 80): 44.3%	

Pedersen, 2018 ⁷³	IFNβ-1a s.c.	n=54	Electronic Autoinjector or	Autoinjector (≥80): 93.0%				
Sabido-Espin, 2017 ⁷⁵	IFNβ-1a s.c	N=5,956	MPR				MPR (≥80): 51.7%	
Sanchirico, 2019 ⁷⁶	GA, IFNβ-1a, IFNβ-1b,	n=7,072	PDC		PDC (≥80): 90.0%			
Settle, 2016 ³⁰	IFNβ-1a i.m.	n=13	IC, MPR				Routine care (IC, MPR): M=0.95, SD=0.11	
Shao, 2018 ⁷⁸	IFNβ-1a, IFNβ-1b, GA	n=6,003	PDC		PDC (≥80): 76.4%			
Solsona, 2017 ⁸⁰	IFNβ-1a s.c.	N=110	Electronic Autoinjector or				Autoinjector (≥80): 90.0%	
Steinberg, 2010 ³⁶	IFNβ-1a, IFNβ-1b	n=1,606	MPR		MPR (≥85): 27.0%	MPR (≥85): 40.0%	MPR (≥85): 41.0%	MPR: M=0.72, SD=0.20

Stockl, 2010 ⁸¹	IFN β -1a, IFN β -1b, GA	<i>n</i> =312	MPR			SP/RP. MPR: <i>M</i> =0.89 <i>SD</i> =0.17
Tan, 2011 ⁸²	IFN β -1a, IFN β -1b, GA	<i>n</i> =2,44 6	MPR			MPR (≥ 80): 59.6%;
Williams, 2018 ⁸⁵	GA	<i>n</i> =109 (Hispan ic); <i>n</i> =139 (Africa n Americ an)	MPR, PDC		Hispanic MPR (≥ 80): 65.1%; PDC (≥ 80): 53.2%.	Hispanic MPR: <i>M</i> =0.80, <i>SD</i> =0.24; PDC: <i>M</i> =0.71, <i>SD</i> =0.28. African American MPR: <i>M</i> =0.80, <i>SD</i> =0.22;

					PDC (≥ 80): 46.0%				PDC: $M=0.67$, $SD=0.29$
Zecca, 2017 ³⁸	IFN β -1a s.c	$n=53$	Electronic Autoinject or			Autoinject tor (< 90%): 28.3%; Autoinject tor (90– 99.9%): 24.0%; Autoinject or (100%): 37.7%			
Zhang, 2017 ⁸⁶	IFN β -1a, IFN β -1b, GA	$N=801$	PDC			PDC (≥ 80): 74.7%			
				Autoinject	MPR: $n=7$, range, 47.0- 77.4%	MPR: $n=7$, range, 35.0- 79.0%	MPR: $n=1$, $M=51.7\%$	Autoinject	MPR: $n=8$, range, 0.69-0.92
				range, 80.5- 93.0%	PDC: $n=6$, range, 46.0- 90.0%	PDC: $n=2$, range, 42.4- 86.0%	PDC: $n=2$, $M=0.95$	IC/MPR: $n=1$, $M=0.95$	PDC: $n=3$, range, 0.67-0.86
				MEMS: $n=1$, $M=82.0\%$				Autoinject or: $n=2$,	

MPR:	67.3-	Autoinjec	range,
<i>n</i> =1,	74.7%	tor: <i>n</i> =4,	0.97-0.98
<i>M</i> =53.0%		range,	
		82.9-	
		95.6%	

M=mean, *SD*=standard deviation, *N*=total sample, *n*=subgroup, NR=not reported

Note: Studies reporting data for multiple subgroups were classified as a single study. Sample sizes included are reported statistics, not total sample, unless specified; Unless otherwise stated, IFNβ-1a and subcutaneous administration. All studies are observational unless otherwise stated. Only baseline and preintervention data are reported for intervention studies. Where required, means and combined excluding IV medications data, using weighted sample group statistics through an online calculator: https://www.statstodo.com/CombineMeansSDs_Pgm.php.

Abbreviations: GA=glatiramer acetate; IC=injection count; IFNβ-1a=interferon beta-1a; IFNβ-1a i.m=interferon beta-1a intramuscular; IFNβ-1a s.c=interferon beta-1a subcutaneous; IFNβ-1b=interferon beta-1b; MEMS=medication event monitoring system; MPR=medication possession ratio; PDC=proportion of days covered; PC=pill count

N=40

SUPPLEMENTARY TABLE 2 Objective adherence rates for oral DMTs

Author, year	DMT(s)	Sample size	Adherence measure	Adherence: Cut-off score (≥80 unless specified)	Adherence: <i>M</i> , <i>SD</i>	Comments
<8 months						

Aungst, 2019 ⁴²	DMF	<i>n</i> =25	PC, MEMS		PC: <i>M</i> =0.91, <i>SD</i> =0.14; MEMS: <i>M</i> =0.90, <i>SD</i> =0.19	Examined adherence over 6-month period; defined pill count as pill count compliance, and measured medication cap compliance via MEMS
Duquette, 2019 ⁹	FTY, DMF, TFN	<i>n</i> =7,305	MPR	MPR (≥80): 74.0%		Examined adherence over 6 months
12 months						
Agashivala, 2013 ⁴¹	FTY	<i>n</i> =248	MPR, PDC	MPR (≥80): 88.9%; PDC (≥80): 70.2%	MPR: <i>M</i> =0.91, <i>SD</i> =0.09; PDC: <i>M</i> =0.81, <i>SD</i> =0.23	New oral DMT users
Aungst, 2019 ⁴²	DMF	<i>n</i> =25	PC, MEMS		PC: <i>M</i> =0.89, <i>SD</i> =0.19; MEMS: <i>M</i> =0.84, <i>SD</i> =0.34	Defined pill count as Pill count compliance, and measures medication cap compliance via MEMS
Burks, 2017 ¹³	FTY, DMF, TFN	<i>n</i> =1,018	PDC	PDC (≥80): 61.4%	PDC: <i>M</i> =0.73, <i>SD</i> =0.29	
Duquette, 2019 ⁹	FTY, DMF, TFN	<i>n</i> =4,567	MPR	MPR (≥80): 73.3%		
Gerber, 2017 ⁵⁹	FTY, DMF, TFN	<i>n</i> =72	MPR	MPR (≥80): 66.7%		

Johnson, 2017 ¹²	FTY, DMF, TFN	N=1,498	PDC, MPR	MPR (≥80): 77.3%; PDC (≥80): 62.9%	MPR: M=0.90, SD=0.14; PDC: M=0.74, SD=0.31	
Sanchirico, 2019 ⁷⁶	FTY, DMF, TFN	n=7,072	PDC	PDC (≥80): 94.0%		
Munsell, 2017 ⁷⁰	FTY, DMF, TFN	n=1,175	MPR	MPR (≥80): 53.0%	MPR: M=0.68, SD=0.30	Newly initiated treatment
Schreiber, 2018 ⁷⁷	FTY	n=126	PC		PC: M=0.99, SD=0.07	Intervention study, but only observational data reported
Vieira, 2019 ⁸³	FTY, TFN	N=4,563	MPR, PDC	MPR (≥80): 89.2%; PDC (≥80): 60.4%	MPR: M=0.92, SD=0.09; PDC: M=0.73, SD=0.28	
Williams, 2018 ⁸⁵	FTY	n=62 (Hispanic); n=71 (African American)	MPR, PDC	Hispanic: MPR (≥80): 80.7%; PDC (≥80): 71.0%. African American: MPR (≥80): 70.4%; PDC (≥80): 63.4%	Hispanic: MPR: M=0.88, SD=0.12; PDC: M=0.83, SD=0.18 African American: MPR: M=0.83, SD=0.20; PDC: M=0.78, SD=0.24	Hispanic and African American subgroups
				MPR: n=7, range, 53.0-89.2%	MPR: n=5, range, 0.68-0.92	
				PDC: n=6, range, 60.4-94.0%	PDC: n=5, range, 0.73-0.83	
					PC: n=2, range, 0.89-0.99	
					MEMS: n=1, 0.84	
24 months						

Duquette, 2019 ⁹	FTY, DMF, TFN	<i>n</i> =3,029	MPR	MPR (≥80): 64.7%	
Zimmer, 2017 ⁸⁸	FTY	<i>N</i> =76	PDC, PC	Perfect (100%): 41.1% Optimal (> 96.2%): 88.2% suboptimal (< 96.2%, but > 85.8%): 11.8%, nonadherent (< 85.8%): 0%	Excluded patients that did not remain on treatment, <i>n</i> =19 recorded as nonpersistent and <i>n</i> =3 as unknown

M=mean, *SD*=standard deviation, *N*=total sample, *n*=subgroup

Note: Studies reporting data for multiple subgroups were classified as a single study. Sample sizes included are reported statistics, not total sample, unless specified. All studies are observational unless otherwise stated. Only baseline and preintervention data are reported for intervention studies. Where required, means and standard deviations were combined excluding IV medications data, using sample group statistics through an online calculator:

https://www.statstodo.com/CombineMeansSDs_Pgm.php.

Abbreviations: DMF=dimethyl fumarate; FTY=fingolimod; MEMS=medication monitoring event system; MPR=medication possession ratio; PC=pill count; PDC=proportion of days covered; TFN=teriflunomide.

N=12

SUPPLEMENTARY TABLE 3 Discontinuation rates for oral and injectable DMTs

Author, year	Definition of discontinuation	Study length	Sample size	DMT(s)	Oral	Injectable	Comments
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<12 Months						
Duquette, 2019 ⁹	>30-day gap	6 months	<i>n</i> =7,712 (oral); <i>n</i> =5,379 (injectable)	IFNβ-1a, IFNβ-1b, GA, FTY, DMF, TFN	FTY, DMF, TFN: 28.0%	IFNβ-1a, IFNβ-1b, GA: 49.0%
Evans, 2012 ⁵⁶	>90-day gap	<6 months	<i>N</i> =1,896	IFNβ-1a, IFNβ-1b, GA		IFNβ-1a, IFNβ-1b, GA: 5.0%
Evans, 2016 ⁵⁵	>90-day gap	<6 months	<i>N</i> =4,830	IFNβ-1a, IFNβ-1b, GA		IFNβ-1a, IFNβ-1b, GA: 9.3%
Stockl, 2010 ⁸¹	>30-day gap	8 months	<i>n</i> =312	IFNβ-1a, IFNβ-1b, GA		SP/RP: 25.0%
					Overall: <i>n</i>=1, 28.0%	Overall: <i>n</i>=4, range, 5.0-49.0%
					>30-day gap: <i>n</i>=1, 28.0%	>30-day gap: <i>n</i>=2, range, 25.0-49.0%
						>90-day gap: <i>n</i>=2, range, 5.0-9.3%
12 Months						
Agashivala, 2013 ⁴¹	> 60-day gap	12 months	<i>n</i> =248 (oral); <i>n</i> =1,643 (injectable)	FTY, IFNβ-1b, IFNβ-1a, GA	1st DMT: FTY: 30.2%. 2nd+ DMT: FTY: 21.1%	1st DMT: IFNβ-1b, IFNβ-1a, GA: 37.0% 2nd+ DMT: IFNβ-1b, IFNβ-1a, GA: 35.0% 1 st DMT are people who started their first DMT; 2 nd + DMT are people who

Burks, 2017 ¹³	>90-day gap	12 months	n=1,018	TFN, FTY, DMF	TFN, FTY, DMF: 16.9%		switched to a subsequent DMT Injectable data contained intravenous, thus, were not included
Cohan, 2018 ⁴⁵	Discontinuation	12 months	N=708	IFNβ-1a, IFNβ-1b		IFNβ-1a, IFNβ-1b: 15.2%	Discontinuation rate for patients stable on any IFN beta therapy
Duquette, 2019 ⁹	>30-day gap	12 months	n=5,995 (oral); n=4,433 (injectable)	IFNβ-1a, IFNβ-1b, GA, FTY, DMF, TFN	FTY, DMF, TFN: 26.3%	IFNβ-1a, IFNβ-1b, GA: 44.0%	
Evans, 2016 ⁵⁵	>90-day gap	12 months	N=4,830	IFNβ-1a, IFNβ-1b, GA		IFNβ-1a, IFNβ-1b, GA: 17.6%	
Munsell, 2017 ⁷⁰	>90-day gap	12 months	n=1,175 (oral); n=7,207 (injectable)	IFNβ-1a, IFNβ-1b, GA, TFN, FTY, DMF	TFN, FTY, DMF: 28.2%	IFNβ-1a, IFNβ-1b, GA: 26.6%	
Prosperini, 2019 ⁷⁴	Discontinuation	12 months	Prematchin g: N=621; PEG, n=196,	PEG, DMF, TFN	DMF, TFN: 15.8%	PEG: 28.6%	Pre and postmatching cohorts examined

			DMF, <i>n</i> =265, TFN, <i>n</i> =160.			
Sabido- Espin, 2017 ⁷⁵	>90-day gap	12 months	<i>N</i> =5,956	IFNβ-1a s.c		IFNβ-1a s.c: 20.6%
Warrender- Sparkes, 2016 ⁸⁴	>90-day gap	12 months	<i>n</i> =45 (oral); <i>n</i> =2,527 (injectable)	IFNβ-1a, IFNβ-1b, GA, FTY	FTY: 10.5%;	IFNβ-1a, IFNβ-1b, GA: 20.6%
Smith, 2015 ⁷⁹	Discontinuation	<i>M</i> =554.2 days	<i>N</i> =8,107	IFNβ-1a		IFNβ-1a: 26.4%
Gerber, 2017 ⁵⁹	>90-day gap	12 months	<i>n</i> =72 (oral); <i>n</i> =2,709 (injectable)	IFNβ-1a, IFNβ-1b, GA, FTY, TFN, DMF	FTY, TFN, DMF: 33.3%	IFNβ-1a, IFNβ-1b, GA: 50.8%
					Overall: <i>n</i> =7, range, 10.5-33.3%	Overall: <i>n</i> =10, range, 15.2%-50.8%
					>30-day gap: <i>n</i> =1, 26.3%	>30-day gap: <i>n</i> =1, 44.0%
					>60-day gap: <i>n</i> =1, range, 21.1%-30.2%	>60-day gap: <i>n</i> =1, range, 35.0%-37.0%
					>90-day gap: <i>n</i> =4, range, 10.5%-33.3%	>90-day gap: <i>n</i> =5, range, 17.6%-50.8%
					Discontinuation: <i>n</i> =1, 15.8%	

Discontinuation: $n=3$, range,
15.2%-28.6%

24 Months

Bonafede, 2013 ³⁹	>59-day gap	24 months	$n=5,710$	IFN β -1a, IFN β -1b, GA		IFNβ-1a, IFNβ-1b, GA: 8.7%	55.3% had a treatment gap >60 days; Fingolimod excluded as an index therapy
Braune, 2016 ⁴³	Discontinuation	24 months; PM: $M=1037.8$ (461.2) days	$N=433$; Propensity matched: $n=198$ (99 FTY, 99 iDMT)	IFN β -1a, IFN β -1b, GA; FTY	FTY: 12.1%	IFNβ-1a, IFNβ-1b, GA: 36.4%	Only provides discontinuation data for propensity matched sample of $n=198$
Condé, 2019 ⁴⁷	Discontinuation	24 months	$N=346$	DMF, TFN	DMF, TFN: 33.1%		
D'Amico, 2019 ⁴⁸	>60-day gap	24 months	$N=903$	DMF, TFN	DMF, TFN: 8.9%		
Duquette, 2019 ⁹	>30-day gap	24 months	$n=3,435$ (oral); $n=4,353$ (injectable)	IFN β -1a, IFN β -1b, GA, FTY, DMF, TFN	FTY, DMF, TFN: 34.0%	IFNβ-1a, IFNβ-1b, GA: 57.0%	
Eriksson, 2018 ⁵²	>60-day gap	Median, 2.5 years	$N=400$	DMF	DMF: 31.0%		

Ernst, 2017⁵³ >30-day gap 24 months *n*=307 IFN β -1a s.c., **DMF: 8.1%** **IFN β -1a s.c: 11.9%**
 (oral); DMF
n=143
 (injectable)

Sabido-Espin, 2017⁷⁵ >90-day gap 24 months *N*=5,956 IFN β -1a s.c **IFN β -1a s.c: 22.6%**

Zimmer, 2017⁸⁸ Discontinuation 24 months *N*=98 FTY **FTY: 1.0%** (complete discontinuation)

19 participants who discontinued fingolimod, eight switched directly to alternative therapy, five interrupted treatment for pregnancy, and six stopped treatment without immediate intention to initiate an alternative treatment. Post hoc analysis showed that all except for one initiated alternative

treatment at a later
time

Fernández-
Fournier,
2015 ⁵⁸ Discontinuation Median: 34 months N=155 GA **GA: 6.3%**

Overall: n=7, range, 1.0%-34.0%
>30-day gap: n=2, range, 8.1%-34.0%
>60-day gap: n=2, range, 8.9%-31.0%
Discontinuation: n=3, range, 1.0%-33.1%
Overall: n=6, range, 6.3%-57.0%
>30-day gap: n=2, range, 11.9%-57.0%
>59-day gap: n=1, 8.7%
>90-day gap: n=1, 22.6%
Discontinuation: n=2, range, 6.3%-36.4%

36 Months +

Lebrun-
Frenay,
2019 ⁶⁵ Discontinuation Up to 5 years n=852 GA **GA: 53.6%**

Sabido-
Espin,
2017 ⁷⁵ >90-day gap 36 months N=5,956 IFNβ-1a s.c. **IFNβ-1a s.c: 30.6%**

Melesse,
2017 ³⁵ >90-day gap M=7.8 years N=721 IFNβ-1a,
IFNβ-1b,
GA **IFNβ-1a, IFNβ-1b, GA: 26.6%**
(complete discontinuation) 57.4% resumed at
some point; 62.6%
discontinued (>90-
days); 26.4%
discontinued for

<1 year; 4.7%
discontinued for
>1 - <2 years;
4.9% discontinued
for >2 - <3 years

Moccia, 2016 ⁶⁸	>90-day gap	>5 years; <i>M</i> =7.9, <i>SD</i> =3.8 years	<i>N</i> =499	IFN β -1a, IFN β -1b	IFNβ-1a, IFNβ-1b: 9.7%	
Evans, 2012 ⁵⁶	>90-day gap	Up to 14 years	<i>n</i> =1,896	IFN β -1a, IFN β -1b, GA	IFNβ-1a, IFNβ-1b, GA: 26.0% (complete discontinuation)	Discontinuation based on initial DMT, accounts for switchers but not those who discontinued following switch; < 6 months: 5.0% discontinuation
Zhornitsky, 2015 ⁸⁷	>90-day gap	Up to 18 years; <i>M</i> =6.1, <i>SD</i> =4.4 years (range 0-	<i>N</i> =1,471	IFN β -1a, IFN β -1b, GA	IFNβ-1a, IFNβ-1b, GA: 19.0% (complete discontinuation)	Recommences did not necessarily recommence an injectable, but may have changed to oral or IV DMT

		18 years follow-up)			
Degil Esposti, 2017 ⁴⁰	Temporary discontinuation < 6-month drug absence; Definitive interruption >12- month drug absence	36 months	<i>N</i> =1,698	IFNβ-1a, IFNβ-1b, GA	IFNβ-1a, IFNβ-1b, GA: Discontinuation (<6 months): 37.0%; Definitive interruption: 28.0%

Overall: *n*=7, range, 9.7%-53.6%
>90-day gap: *n*=5, range, 9.7%-
30.6%
<6-month absence: *n*=1, 37.0%
>12-month absence: *n*=1, 28.0%
Discontinuation: *n*=1, 53.6%

N=total sample, *n*=subgroup, *M*=mean, *SD*=standard deviation

Note: Studies reporting data for multiple subgroups were classified as a single study. Unless otherwise stated, IFNβ-1a includes both intramuscular and subcutaneous administration. All studies are observational unless otherwise stated. Where required, means and standard deviations were combined excluding IV medications data, using sample group statistics through an online calculator: https://www.statstodo.com/CombineMeansSDs_Pgm.php.

Abbreviations: DMF=dimethyl fumarate; DMT=disease-modifying therapy; FTY=fingolimod; GA=glatiramer acetate; IFNβ-1a=interferon beta-1a; IFNβ-1a i.m=interferon beta-1a intramuscular; IFNβ-1a s.c.=interferon beta-1a subcutaneous; IFNβ-1b=interferon beta-1b; MS=multiple sclerosis; PEG=pegylated Interferon; PM=propensity matched; RP=retail pharmacy; RRMS=relapse remitting multiple sclerosis; SP=speciality pharmacy; TFN=teriflunomide.

SUPPLEMENTARY TABLE 4 Appraisal tool for cross-sectional studies (AXIS) for included objective studies

AXIS Criteria					
Intro	Methods	Results	Discussion	Other	Total

D'Amico, 2019 ⁴⁸	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	17
Defer, 2018 ⁴⁹	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NP	12
Deftereos , 2018 ⁵⁰	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	17
Degil Esposti, 2017 ⁴⁰	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	NP	14
Devonshi re, 2016 ⁵¹	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	16
Duquette , 2019 ⁹	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	N	Y	N	N/A	N/A	Y	Y	Y	Y	Y	NR	11
Eriksson, 2018 ⁵²	Y	Y	N/A	Y	Y	Y	N	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	16
Ernst, 2017 ⁵³	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NR	14
Evans, 2017 ⁵⁴	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	16
Evans, 2016 ⁵⁵	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	16
Evans, 2012 ⁵⁶	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	16
Fernández, 2016 ⁵⁷	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	16

Lugaresi, 2012 ⁶⁶	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	17
McKay, 2017 ⁶⁷	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	19
Melesse, 2017 ³⁵	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	16
Moccia, 2016 ⁶⁸	Y	Y	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	17
Moccia, 2015 ⁶⁹	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	17
Munsell, 2017 ⁷⁰	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	NR	15
Oleen- Burkey, 2011 ⁷¹	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NP	12
Paolicelli , 2016 ⁷²	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	17
Pedersen, 2018 ⁷³	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	17
Prosperin i, 2019 ⁷⁴	Y	Y	N/A	Y	Y	Y	N/A	Y	N	Y	N	Y	N/A	N/A	Y	Y	Y	Y	N	Y	14
Sabido- Espin, 2017 ⁷⁵	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NR	13

Sanchirico, 2019 ⁷⁶	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	N	Y	Y	N/A	N/A	Y	N	Y	Y	Y	Y	12
Schrieber, 2018 ⁷⁷	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	18
Settle, 2016 ³⁰	Y	Y	N	Y	N	N	N	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	Y	Y	11
Shao, 2018 ⁷⁸	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	N	Y	Y	N/A	N/A	Y	Y	Y	Y	N	NP	13
Smith, 2015 ⁷⁹	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NR	13
Solsona, 2017 ⁸⁰	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	N	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	15
Steinberg, 2010 ³⁶	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NP	12
Stockl, 2010 ⁸¹	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	NR	15
Tan, 2011 ⁸²	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NP	12
Vieira, 2019 ⁸³	Y	Y	N/A	Y	Y	N	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NR	12
Warrender-Sparkes, 2016 ⁸⁴	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	16

Williams, 2018 ⁸⁵	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	NR	13
Zecca, 2017 ³⁸	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	15
Zhang, 2017 ⁸⁶	Y	Y	N/A	Y	Y	Y	N/A	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	Y	N	Y	16
Zhornitskiy, 2015 ⁸⁷	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	N/A	N/A	Y	Y	Y	N	N	Y	14
Zimmer, 2017 ⁸⁸	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	18

TOTAL (%)	Y: 60 (98.4 %); N: 1 (1.6%)	Y: 60 (98.4 %); N: 1 (1.6%)	Y: 8 (13.1%)	Y: 61 (100.0%)	Y: 59 (96.7 %); N: 2 (3.3%)	Y: 56 (91.8 %); N: 5 (8.2%)	Y: 13 (21.3 %); N: 7 (11.5%)	Y: 61 (100.0 %); N: 0 (0.0%)	Y: 58 (95.1 %); N: 3 (4.9%)	Y: 54 (88.5 %); N: 7 (11.5%)	Y: 59 (96.8 %); N: 2 (3.3%)	Y: 59 (96.8 %); N: 2 (3.3%)	N/A: 45 (73.8 %); N: 16 (26.2%)	Y: 12 (19.7 %); N: 4 (6.6%)	Y: 61 (100.0 %); N: 1 (1.6%)	Y: 60 (98.4 %); N: 1 (1.6%)	Y: 61 (100.0 %); N: 1 (1.6%)	Y: 58 (95.1 %); N: 3 (4.9%)	Y: 37 (60.7 %); N: 24 (39.3%)	Y: 38 (62.3 %); N: 23 (37.7%)
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Note: For total scores of each question, responses were assigned either a positive value (+1), negative value (-1) or neutral value (0), relative to specific questions. Items 1-12 were coded, Y=1 N=0, N/A=0; Items 13 and 19 were coded, Y=-1; N=1, N/A=0; and item 20 was coded, Y=1, NP=-1, NR=0.

Abbreviations: Y=yes; N=no, N/A=not applicable, NP=not provided, NR=not required.

Criteria: 1. Were the aims/objective of the study clear? 2. Was the study design appropriate for the stated aim(s)?; 3. Was the sample size justified?; 4. Was the target/reference population clearly defined? (Is it clear who the research was about?); 5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?; 6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?; 7. Were measures undertaken to address and categorize Nonresponders?; 8. Were the risk factor and outcome variables measured appropriate to the aims of the study?; 9. Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted or published previously?; 10. Is it clear what was used to determine statistical significance and/or precision estimates? (eg, *P*-values, CI); 11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?; 12. Were the basic data adequately described?; 13. Does the response rate raise concerns about Nonresponse bias?; 14. If appropriate, was information about Nonresponders described?; 15. Were the results internally consistent?; 16. Were the results presented for all the analyses described in the methods?; 17. Were the authors' discussions and conclusions justified by the results?; 18. Were the limitations of the study discussed?; 19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?; 20. Was ethical approval or consent of participants attained?

N=61

SUPPLEMENTARY TABLE 5 Sensitivity analysis to check effect of excluding studies with highest weights in meta-analyses

Excluded study	Pooled ES	LCI 95%	HCI 95%	Cochran Q	p	I²	I² LCI 95%	I² HCI 95%
Mean adherence rate (oral DMTs)								
Agashivala, 2013 ⁴¹	0.91	0.80	1.03	765.99	0.00	99.48	99.31	99.61
Johnson, 2017 ¹²	0.91	0.75	1.08	753.13	0.00	99.47	99.29	99.60
Munsell, 2017 ⁷⁰	0.92	0.89	0.94	47.96	0.00	91.66	83.52	95.78
Vieira, 2019 ⁸³	0.88	0.76	1.00	584.28	0.00	99.32	99.07	99.50
Williams, 2018 (Hispanic) ⁸⁵	0.91	0.82	1.01	761.64	0.00	99.47	99.30	99.60
Williams, 2018 (African American) ⁸⁵	0.91	0.82	1.01	754.10	0.00	99.47	99.30	99.60
Mean adherence rate (injectable DMTs)								
Agashivala, 2013 ⁴¹	0.72	0.63	0.81	421.87	0.00	98.58	98.03	98.97
Cerghet, 2010 ⁴⁴	0.77	0.66	0.87	1416.17	0.00	99.58	99.47	99.66
Kleinman, 2010 ⁶¹	0.77	0.66	0.88	1413.11	0.00	99.58	99.47	99.66
Munsell, 2017 ⁷⁰	0.82	0.71	0.92	645.82	0.00	99.07	98.77	99.30
Steinberg, 2010 ³⁶	0.78	0.64	0.92	1307.67	0.00	99.54	99.43	99.63
Stockl, 2010 ⁸¹	0.76	0.65	0.87	1243.25	0.00	99.52	99.40	99.61
Williams, 2018 (Hispanic) ⁸⁵	0.77	0.66	0.87	1414.32	0.00	99.58	99.47	99.66
Williams, 2018 (African American) ⁸⁵	0.77	0.66	0.87	1413.21	0.00	99.58	99.47	99.66
Mean discontinuation rate (oral DMTs)								
Agashivala, 2013 (1st DMT) ⁴¹	0.24	0.17	0.32	97.20	0.00	93.83	89.68	96.31
Agashivala, 2013 (2nd+ DMT) ⁴¹	0.24	0.17	0.32	99.72	0.00	93.98	89.98	96.39
Burks, 2017 ¹³	0.26	0.19	0.33	54.47	0.00	88.98	79.78	94.00
Duquette, 2019 ⁹	0.21	0.14	0.28	70.90	0.00	91.54	85.14	95.18
Munsell, 2017 ⁷⁰	0.24	0.15	0.33	91.58	0.00	93.45	88.95	96.12
Prosperini, 2019 ⁷⁴	0.25	0.18	0.32	76.44	0.00	92.15	86.38	95.48
Warrender-Sparkes, 2016 ⁸⁴	0.24	0.18	0.31	92.07	0.00	93.48	89.02	96.13

Gerber, 2017 ⁵⁹	0.24	0.17	0.31	98.71	0.00	93.92	89.86	96.35
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Mean discontinuation rate (injectable DMTs)

Agashivala, 2013 (1st DMT) ⁴¹	0.26	0.19	0.34	1757.89	0.00	99.49	99.38	99.58
Agashivala, 2013 (2nd+ DMT) ⁴¹	0.26	0.19	0.34	1783.63	0.00	99.50	99.39	99.58
Cohan, 2018 ⁴⁵	0.27	0.20	0.35	1759.61	0.00	99.49	99.38	99.58
Duquette, 2019 ⁹	0.25	0.18	0.32	1249.17	0.00	99.28	99.11	99.42
Evans, 2016 ⁵⁵	0.28	0.21	0.36	1505.15	0.00	99.40	99.27	99.51
Munsell, 2017 ⁷⁰	0.27	0.18	0.35	1834.58	0.00	99.51	99.41	99.59
Prosperini, 2019 ⁷⁴	0.27	0.19	0.34	1834.33	0.00	99.51	99.41	99.59
Sabido-Espin, 2017 ⁷⁵	0.28	0.20	0.36	1669.27	0.00	99.46	99.35	99.55
Warrender-Sparkes, 2016 ⁸⁴	0.27	0.19	0.35	1771.92	0.00	99.49	99.39	99.58
Smith, 2015 ⁷⁹	0.27	0.18	0.36	1834.07	0.00	99.51	99.41	99.59
Gerber, 2017 ⁵⁹	0.25	0.19	0.32	1173.51	0.00	99.23	99.05	99.38

Adherence as dichotomous outcomes ($\geq 80\%$ adherence)

Excluded study	Pooled prevalence	LCI 95%	HCI 95%	Cochran Q	p	I ²	I ² LCI 95%	I ² HCI 95%
(A) Oral DMT, MPR								
Agashivala, 2013 ⁴¹	0.79	0.59	0.95	821.04	0.00	99.39	99.21	99.53
Duquette, 2019 ⁹	0.83	0.48	1.00	685.65	0.00	99.27	99.03	99.45
Gerber, 2017 ⁵⁹	0.79	0.60	0.95	832.60	0.00	99.40	99.22	99.54
Munsell, 2017 ⁷⁰	0.82	0.66	0.95	419.59	0.00	98.81	98.34	99.15
Vieira, 2019 ⁸³	0.70	0.49	0.90	229.33	0.00	97.82	96.72	98.55
Williams, 2018 (Hispanic) ⁸⁵	0.79	0.60	0.95	838.60	0.00	99.40	99.22	99.54
Williams, 2018 (African American) ⁸⁵	0.79	0.60	0.95	835.49	0.00	99.40	99.22	99.54
(B) Injectable DMTs, MPR								
Agashivala, 2013 ⁴¹	0.61	0.49	0.72	808.54	0.00	99.26	99.04	99.43

Degli Esposti, 2017 ⁴⁰	0.62	0.49	0.74	1001.64	0.00	99.40	99.24	99.53
Duquette, 2019 ⁹	0.64	0.53	0.75	718.53	0.00	99.16	98.90	99.36
Evans, 2017 ⁵⁴	0.58	0.47	0.69	524.35	0.00	98.86	98.45	99.15
Gerber, 2017 ⁵⁹	0.62	0.48	0.75	1008.16	0.00	99.40	99.24	99.53
Munsell, 2017 ⁷⁰	0.66	0.55	0.77	716.79	0.00	99.16	98.90	99.36
Williams, 2018 (Hispanic) ⁸⁵	0.62	0.51	0.73	1007.81	0.00	99.40	99.24	99.53
Williams, 2018 (African American) ⁸⁵	0.62	0.51	0.73	1008.19	0.00	99.40	99.24	99.53

(C) Oral DMTs, PDC

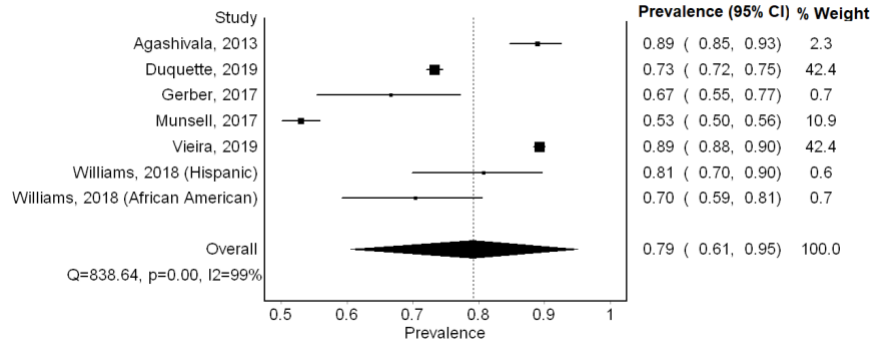
Agashivala, 2013 ⁴¹	0.80	0.51	1.00	2586.91	0.00	99.81	99.77	99.84
Burks, 2017 ¹³	0.81	0.50	1.00	2413.68	0.00	99.79	99.75	99.83
Johnson, 2017 ¹²	0.82	0.48	1.00	2356.84	0.00	99.79	99.75	99.82
Sanchirico, 2019 ⁷⁶	0.61	0.58	0.65	14.25	0.01	64.91	15.58	85.41
Vieira, 2019 ⁸³	0.87	0.54	1.00	1353.78	0.00	99.63	99.54	99.70
Williams, 2018 (Hispanic) ⁸⁵	0.80	0.52	1.00	2597.14	0.00	99.81	99.77	99.84
Williams, 2018 (African American) ⁸⁵	0.80	0.52	1.00	2589.98	0.00	99.81	99.77	99.84

(D) Injectable DMTs, PDC

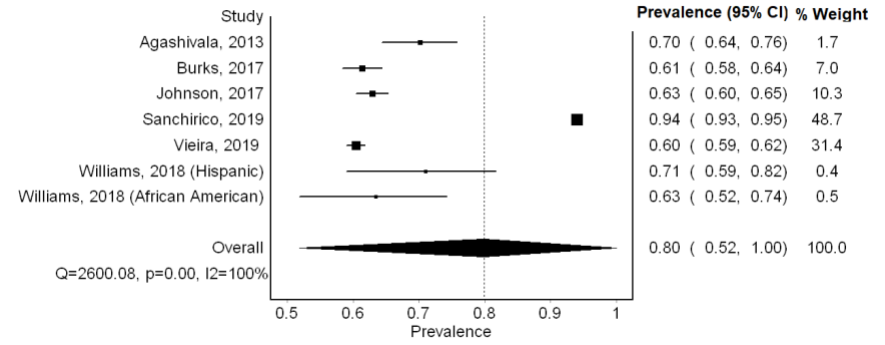
Agashivala, 2013 ⁴¹	0.82	0.71	0.91	718.98	0.00	99.30	99.08	99.47
Evans, 2016 ⁵⁵	0.81	0.61	0.97	1405.08	0.00	99.64	99.56	99.71
Melesse, 2017 ³⁵	0.80	0.65	0.92	1444.73	0.00	99.65	99.57	99.72
Sanchirico, 2019 ⁷⁶	0.73	0.60	0.85	526.28	0.00	99.05	98.70	99.30
Shao, 2018 ⁷⁸	0.81	0.61	0.97	1391.49	0.00	99.64	99.55	99.71
Williams, 2018 (Hispanic) ⁸⁵	0.80	0.66	0.92	1408.76	0.00	99.65	99.56	99.72
Williams, 2018 (African American) ⁸⁵	0.80	0.67	0.92	1372.99	0.00	99.64	99.54	99.71

SUPPLEMENTARY FIGURE 1 Forest plot showing pooled estimates for the proportion of sample oral and injectable DMTs showing adherence of more than 80%, with separate subgroups for MPR and PDC

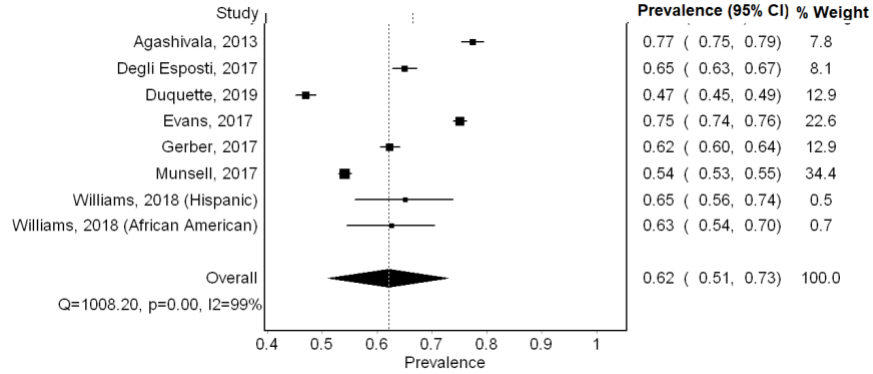
Oral DMTs MPR



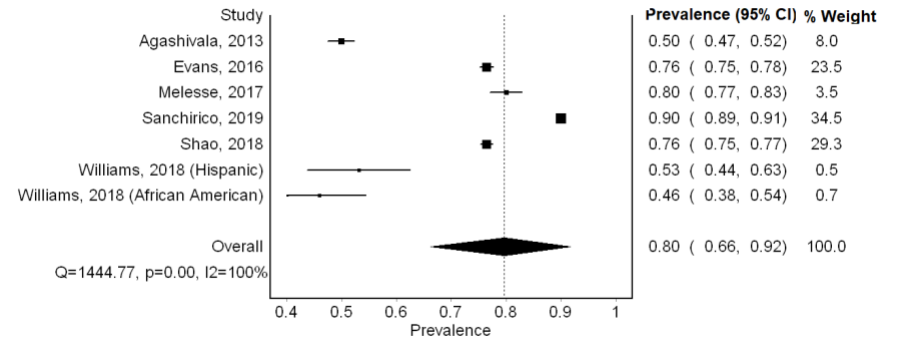
Oral DMTs PDC



Injectable DMTs MPR



Injectable DMTs PDC



SUPPLEMENTARY FIGURE 2 Doi plot showing major asymmetry between all studies

