Appendix Materials

Appendix Table 1: N-of-1 Trial Searches

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomized controlled trials/
4.	Double-blind Method/
5.	Single-Blind Method/
6.	clinical trial.pt.
7.	Clinical Trials.mp. or exp Clinical Trials/
8.	random$.tw.
9.	trial$.tw.
10.	Cross-Over Studies/
11.	or/1-10
12.	n-of-1.af.
13.	11 and 12
14.	(single-subject or single-patient or single case or single-case or within-patient).af.
15.	((single adj1 patient) or (single adj1 subject)).tw.
16.	14 or 15
17.	12 and 16
18.	multi-crossover.mp.
19.	12 and 18
20.	13 or 17 or 19
21.	limit 19 to yr="2010 - 2017"

Appendix Table 2: Repeated Period Crossover Trials

1.	(repeat$ or rotat$).af.
2.	((three or four or five or six) and period).tw.
3.	(multi- or multiple).tw.
4.	(three-period or four-period or five-period or six-period).tw.
5.	(three-way or four-way or five-way or six-way).tw.
6.	or/1-5
7.	Cross-Over Studies/ or (cross-over or crossover).af.
8.	6 and 7
9.	randomized controlled trial.pt.
10.	controlled clinical trial.pt.
11.	randomized controlled trials/
12.	Double-blind Method/
13.	Single-Blind Method/
14.	clinical trial.pt.
15.	Clinical Trials.mp. or exp Clinical Trials/
16.	random$.tw.
17.	trial$.tw.
18.	or/9-17
19.	8 and 18
20.	(dt or de or tu).fs.
21.	19 and 20
22.	7 and 20
23.	"Reproducibility of Results"/
24.	16 and 22
25.	limit 22 to english language
26.	9 or 10 or 11 or 14 or 15 or 16
27.	7 or 23
28.	20 and 26 and 27
29.	random.af.
30.	9 or 10 or 11 or 14 or 15 or 29
31.	ae.fs.
32.	20 or 31
33.	27 and 30 and 32
34.	limit 33 to (english language and humans)
35.	periods.af.

36.	6 or 35
37.	33 and 36
38.	Animals/ not human/
39.	37 not 38

Appendix Table 3: Reference List of Included Studies

1.	Nikles CJ, McKinlay L, Mitchell GK, Carmont SA, Senior HE, Waugh MC et al. Aggregated n-of-1 trials of central nervous system stimulants versus placebo for paediatric traumatic brain injury--a pilot study. Trials [Electronic Resource] 2014; 15:54.
2.	Tison F, Negre-Pages L, Meissner WG, Dupouy S, Li Q, Thiolat ML et al. Simvastatin decreases levodopa-induced dyskinesia in monkeys, but not in a randomized, placebo-controlled, multiple cross-over ("n-of-1") exploratory trial of simvastatin against levodopa-induced dyskinesia in Parkinson's disease patients. Parkinsonism & Related Disorders 2013; 19(4):416-421.
3.	Rascol O, Ferreira J, Negre-Pages L, Perez-Lloret S, Lacomblez L, Galitzky M et al. A proof-of-concept, randomized, placebo-controlled, multiple cross-overs (n-of-1) study of naftazone in Parkinson's disease. Fundamental & Clinical Pharmacology 2012; 26(4):557-564.
4.	Emmanuel AV, Kamm MA, Roy AJ, Kerstens R, Vandeplassche L. Randomised clinical trial: the efficacy of prucalopride in patients with chronic intestinal pseudo-obstruction--a double-blind, placebo-controlled, cross-over, multiple n = 1 study. Alimentary Pharmacology & Therapeutics 2012; 35(1):48-55.
5.	Yelland MJ, Poulos CJ, Pillans PI, Bashford GM, Nikles CJ, Sturtevant JM et al. N-of-1 randomized trials to assess the efficacy of gabapentin for chronic neuropathic pain. Pain Medicine 2009; 10(4):754-761.
6.	Nonoyama ML, Brooks D, Guyatt GH, Goldstein RS. Effect of oxygen on health quality of life in patients with chronic obstructive pulmonary disease with transient exertional hypoxemia. American Journal of Respiratory & Critical Care Medicine 2007; 176(4):343-349.
7.	Huber AM, Tomlinson GA, Koren G, Feldman BM. Amitriptyline to relieve pain in juvenile idiopathic arthritis: a pilot study using Bayesian metaanalysis of multiple N-of-1 clinical trials. Journal of Rheumatology 2007; 34(5):1125-1132.
8.	Yelland MJ, Nikles CJ, McNairn N, Del Mar CB, Schluter PJ, Brown RM. Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials. Rheumatology 2007; 46(1):135-140.
9.	Zucker DR, Ruthazer R, Schmid CH, Feuer JM, Fischer PA, Kieval RI et al. Lessons learned combining N-of-1 trials to assess fibromyalgia therapies. Journal of Rheumatology 2006; 33(10):2069-2077.
10.	Nikles CJ, Mitchell GK, Del Mar CB, Clavarino A, McNairn N. An n-of-1 trial service in clinical practice: testing the effectiveness of stimulants for attention-deficit/hyperactivity disorder. Pediatrics 2006; 117(6):2040-2046.
11.	Nathan PC, Tomlinson G, Dupuis LL, Greenberg ML, Ota S, Bartels U et al. A pilot study of ondansetron plus metopimazine vs. ondansetron monotherapy in children receiving highly emetogenic chemotherapy: a Bayesian randomized serial N-of-1 trials design. Supportive Care in Cancer 2006; 14(3):268-276.
12.	Pereira JA, Holbrook AM, Dolovich L, Goldsmith C, Thabane L, Douketis JD et al. Are brand-name and generic warfarin interchangeable? Multiple n-of-1 randomized, crossover trials. Annals of Pharmacotherapy 2005; 39(7-8):1188-1193.
13.	Woodfield R, Goodyear-Smith F, Arroll B. N-of-1 trials of quinine efficacy in skeletal muscle cramps of the leg. British Journal of General Practice 2005; 55(512):181-185.
14.	Wegman AC, van der Windt DA, Bongers M, Twisk JW, Stalman WA, de Vries TP. Efficacy of temazepam in frequent users: a series of N-of-1 trials. Family Practice 2005; 22(2):152-159.
15.	Nikles CJ, Yelland M, Glasziou PP, Del MC. Do individualized medication effectiveness tests (n-of-1 trials) change clinical decisions about which drugs to use for osteoarthritis and chronic pain?. [Review] [19 refs]. American Journal of Therapeutics 2005; 12(1):92-97.
16.	Smith BJ, Appleton SL, Veale AJ, McElroy HJ, Veljkovic D, Saccoia L. Eformoterol n-of-1 trials in chronic obstructive pulmonary disease poorly reversible to salbutamol. Chronic Respiratory Disease 2004; 1(2):63-69.

17.	Haas DC, Sheehe PR. Dextroamphetamine pilot crossover trials and n of 1 trials in patients with chronic tension-type and migraine headache. Headache 2004; 44(10):1029-1037.
18.	Mandelcorn J, Cullen NK, Bayley MT. A preliminary study of the efficacy of ondansetron in the treatment of ataxia, poor balance and incoordination from brain injury. Brain Injury 2004; 18(10):1025-1039.
19.	Pope JE, Prashker M, Anderson J. The efficacy and cost effectiveness of N of 1 studies with diclofenac compared to standard treatment with nonsteroidal antiinflammatory drugs in osteoarthritis. Journal of Rheumatology 2004; 31(1):140-149.
20.	Wegman AC, van der Windt DA, de HM, Deville WL, Fo CT, de Vries TP. Switching from NSAIDs to paracetamol: a series of n of 1 trials for individual patients with osteoarthritis. Annals of the Rheumatic Diseases 2003; 62(12):1156-1161.
21.	Reitberg DP, Del RE, Weiss SL, Rebell G, Zaias N. Single-patient drug trial methodology for allergic rhinitis. Annals of Pharmacotherapy 2002; 36(9):1366-1374.
22.	Linday LA, Tsiouris JA, Cohen IL, Shindledecker R, DeCresce R. Famotidine treatment of children with autistic spectrum disorders: pilot research using single subject research design. Journal of Neural Transmission 2001; 108(5):593-611.
23.	Duggan CM, Mitchell G, Nikles CJ, Glasziou PP, Del Mar CB, Clavarino A. Managing ADHD in general practice. N of 1 trials can help! Australian Family Physician 2000; 29(12):1205-1209.
24.	Nikles CJ, Glasziou PP, Del Mar CB, Duggan CM, Clavarino A, Yelland MJ. Preliminary experiences with a single-patient trials service in general practice. Medical Journal of Australia 2000; 173(2):100-103.
25.	Mahon JL, Laupacis A, Hodder RV, McKim DA, Paterson NA, Wood TE et al. Theophylline for irreversible chronic airflow limitation: a randomized study comparing n of 1 trials to standard practice. Chest 1999; 115(1):38-48.
26.	Bollert FG, Paton JY, Marshall TG, Calvert J, Greening AP, Innes JA. Recombinant DNase in cystic fibrosis: a protocol for targeted introduction through n-of-1 trials. Scottish Cystic Fibrosis Group. European Respiratory Journal 1999; 13(1):107-113.
27.	Kent MA, Camfield CS, Camfield PR. Double-blind methylphenidate trials: practical, useful, and highly endorsed by families. Archives of Pediatrics & Adolescent Medicine 1999; 153(12):1292-1296.
28.	Webb S, Tansey P, Brown H, Jackson A, Bilton D. Placebo-controlled n-of-1 trials in cystic fibrosis. European Respiratory Journal 1999; 14(4):993.
29.	Haines DR, Gaines SP. N of 1 randomised controlled trials of oral ketamine in patients with chronic pain. Pain 1999; 83(2):283-287.
30.	Sheather-Reid RB, Cohen M. Efficacy of analgesics in chronic pain: a series of N-of-1 studies. Journal of Pain & Symptom Management 1998; 15(4):244-252.
31.	Camfield P, Gordon K, Dooley J, Camfield C. Melatonin appears ineffective in children with intellectual deficits and fragmented sleep: six "N of 1" trials. Journal of Child Neurology 1996; 11(4):341-343.
32.	Mahon J, Laupacis A, Donner A, Wood T. Randomised study of n of 1 trials versus standard practice.[Erratum appears in BMJ 1996 Jun 1;312(7043):1392]. BMJ 1996; 312(7038):1069-1074.
33.	Maier W, Benkert O. Treatment of chronic depression with sulpiride: evidence of efficacy in placebo-controlled single case studies. Psychopharmacology 1994; 115(4):495-501.
34.	McQuay HJ, Carroll D, Jadad AR, Glynn CJ, Jack T, Moore RA et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomised controlled crossover trial with integral n-of-1 design. Pain 1994; 59(1):127-133.
35.	March L, Irwig L, Schwarz J, Simpson J, Chock C, Brooks P. n of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthritis. BMJ 1994; 309(6961):1041-1045.
36.	Denburg SD, Carbotte RM, Denburg JA. Corticosteroids and neuropsychological functioning in

	patients with systemic lupus erythematosus. Arthritis & Rheumatism 1994; 37(9):1311-1320.
37.	Privitera MD, Treiman DM, Pledger GW, Sahlroot JT, Handforth A, Linde MS et al. Dezinamide for partial seizures: results of an n-of-1 design trial. Neurology 1994; 44(8):1453-1458.
38.	Langer JC, Winthrop AL, Issenman RM. The single-subject randomized trial. A useful clinical tool for assessing therapeutic efficacy in pediatric practice. Clinical Pediatrics 1993; 32(11):654-657.
39.	Molloy DW, Guyatt GH, Standish T, Willan A, McIlroy W, D'Souza J et al. Effect of a new nootropic agent, CGS 5649B, on cognition, function, and behavior in dementia. Journal of General Internal Medicine 1993; 8(8):444-447.
40.	Johannessen T, Petersen H, Kristensen P, Fosstvedt D, Kleveland PM, Dybdahl J et al. Cimetidine on-demand in dyspepsia. Experience with randomized controlled single-subject trials. Scandinavian Journal of Gastroenterology 1992; 27(3):189-195.
41.	Johannessen T, Kristensen P, Petersen H, Fosstvedt D, Loge I, Kleveland PM et al. The symptomatic effect of 1-day treatment periods with cimetidine in dyspepsia. Combined results from randomized, controlled, single-subject trials. Scandinavian Journal of Gastroenterology 1991; 26(9):974-980.
42.	Patel A, Jaeschke R, Guyatt GH, Keller JL, Newhouse MT. Clinical usefulness of n-of-1 randomized controlled trials in patients with nonreversible chronic airflow limitation. American Review of Respiratory Disease 1991; 144(4):962-964.
43.	Larsen S, Farup P, Flaten O, Osnes M. The multi-crossover model for classifying patients as responders to a given treatment. Scandinavian Journal of Gastroenterology 1991; 26(7):763-770.
44.	Jaeschke R, Adachi J, Guyatt G, Keller J, Wong B. Clinical usefulness of amitriptyline in fibromyalgia: the results of 23 N-of-1 randomized controlled trials. Journal of Rheumatology 1991; 18(3):447-451.
45.	Hinderer SR. The supraspinal anxiolytic effect of baclofen for spasticity reduction. American Journal of Physical Medicine & Rehabilitation 1990; 69(5):254-258.
46.	Lashner BA, Hanauer SB, Silverstein MD. Testing nicotine gum for ulcerative colitis patients. Experience with single-patient trials. Digestive Diseases & Sciences 1990; 35(7):827-832.
47.	McBride MC. An individual double-blind crossover trial for assessing methylphenidate response in children with attention deficit disorder. Journal of Pediatrics 1988; 113(1:Pt 1):t-45.
48.	Menard J, Serrurier D, Bautier P, Plouin PF, Corvol P. Crossover design to test antihypertensive drugs with self-recorded blood pressure. Hypertension 1988; 11(2):153-159.
49.	Ullmann RK, Sleator EK. Responders, nonresponders, and placebo responders among children with attention deficit disorder. Importance of a blinded placebo evaluation. Clinical Pediatrics 1986; 25(12):594-599.
50.	Wolfe B, Del RE, Weiss SL, Mendelson A, Elbaga TA, Huser FJ et al. Validation of a single-patient drug trial methodology for personalized management of gastroesophageal reflux disease. J Manag Care Pharm 2002; 8(6):459-468.
51.	Brookes ST, Biddle L, Paterson C, Woolhead G, Dieppe P. "Me's me and you's you": Exploring patients' perspectives of single patient (n-of-1) trials in the UK. Trials 2007; 8:10.
52.	Wallace AE, Kofoed LL. Statistical Analysis of Single Case Studies in the Clinical Setting: The Example of Methylphenidate Trials in Children with Attention-Deficit Hyperactivity Disorder. Journal of Child and Adolescent Psychopharmacology 1994; 4(3):141-150.
53.	Miyazaki S, Nonogi H, Goto Y, Sumiyoshi T, Haze K, Hiramori K. Comparison of the therapeutic efficacy of continuous and intermittent injection of isosorbide dinitrate: a randomized study on unstable angina. Internal Medicine 1995; 34(9):856-862.
54,	Parodi O, Maseri A, Simonetti I. Management of unstable angina at rest by verapamil. A double-blind cross-over study in coronary care unit. British Heart Journal 1979; 41(2):167-174.
55.	Parodi O, Simonetti I, Michelassi C, Carpeggiani C, Biagini A, L'Abbate A et al. Comparison of verapamil and propranolol therapy for angina pectoris at rest: a randomized, multiple-crossover, controlled trial in the coronary care unit. American Journal of Cardiology 1986; 57(11):899-906.

56.	Joy TR, Zou GY, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. Annals of internal medicine 2014 Oct 7;161(7):531-2
57.	Lipka AF, Vrinten C, van Zwet EW, Schimmel KJM, Cornel MC, Kuijpers MR, et al. Ephedrine treatment for autoimmune myasthenia gravis. Neuromuscular disorders 2017; 27:259-265.
58.	McGarry ME, Illek B, Ly NP, Zlock L, Olshansky S, Moreno C, et al. In vivo and in vitro ivacaftor response in cystic fibrosis patients with residual CFTR function: n-of-1 studies. Pediatric pulmonology 2017;52(4):472-9.
59.	Mitchell GK, Hardy JR, Nikles CJ, Carmont SA, Senior HE, Schluter PJ, et al. The Effect of Methylphenidate on Fatigue in Advanced Cancer: An Aggregated N-of-1 Trial. Journal of pain and symptom management 2015 Sep;50(3):289-96.
60.	Nikles J, Mitchell GK, Hardy J, Agar M, Senior H, Carmont SA, et al. Testing pilocarpine drops for dry mouth in advanced cancer using n-of-1 trials: A feasibility study. Palliative Medicine 2015 Dec;29(10):967-74.
61.	Nikles J, Mitchell GK, Hardy J, Senior H, Carmont SA, Schluter PJ, et al. Single-patient multiple crossover studies to determine the effectiveness of paracetamol in relieving pain suffered by patients with advanced cancer taking regular opioids: A pilot study. 2016;30(8):800-2.
62.	Nikles J, Mitchell G, McKinlay L, Waugh MC, Epps A, Carmont SA, et al. A series of n-of-1 trials of stimulants in brain injured children. 2017;40(1):11-21.

Appendix Table 4: Risk of bias assessment

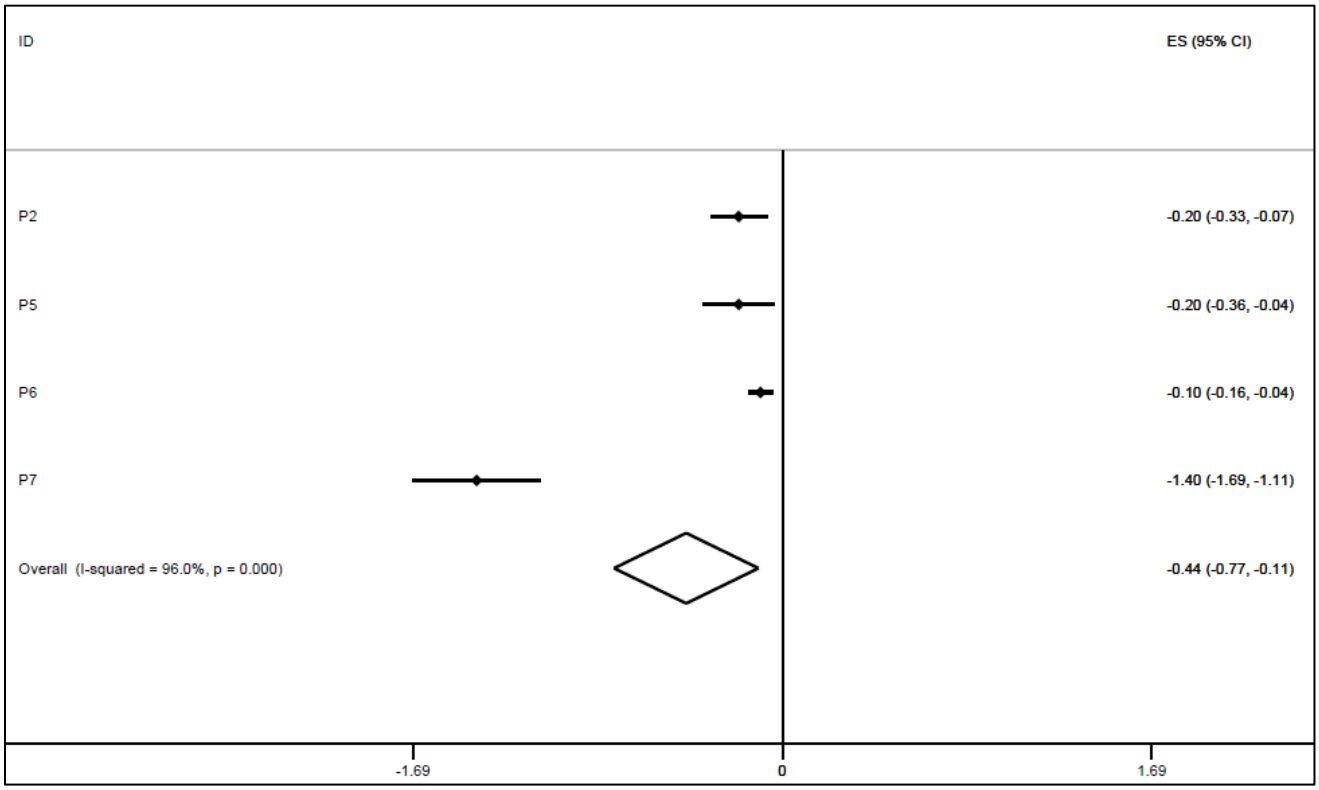
Author Yr	1. Randomization adequate?	2. Allocation concealed?	3. Patient blinded?	4. Outcome assessor blinded?	5. run-in period?	7. Wash-out?	8. Statistical methods appropriate?*	9. All randomized participants analyzed?	10. Incomplete outcome data
Nikles 2014	Low	Low	Low	Low	High	High	Low	High	Low
Tison 2013	Unclear	Low	Low	Low	High	Low	High	Low	Low
Rascol 2012	Unclear	Unclear	Low	Low	Low	Low	Low	High	Low
Emmanuel 2012	Unclear	Unclear	Low	Low	High	High	High	High	Low
Yelland 2009	Low	Low	Low	Low	High	High	Low	High	Low
Brookes 2007	Low	Low	Low	Low	High	High	unclear	High	Low
Nonoyama2007	Low	Low	Low	Low	High	High	unclear	High	Low
Huber 2007	Low	Low	Low	Low	High	Low	High	Low	Low
Yelland 2007	Low	Unclear	Low	Low	High	High	Low	High	Low
Zucker 2006	Low	Unclear	Low	Low	Low	High	Low	High	Low
Nikles 2006	Low	Unclear	Low	Low	High	Low	High	High	Low
Nathan 2006	Low	Low	Low	Low	High	High	High	High	Low
Pereira 1995	Unclear	Low	Low	Low	High	High	High	Low	Low
Woodfield 2005	Low	Low	Low	Low	Low	Low	Low	Low	Low
Wegman 2005	Low	Unclear	Low	Low	High	High	Low	High	Low
Nikles 2005	Low	Unclear	Low	Low	High	Low	High	High	Low
Smith 2004	Low	Low	Low	Low	Low	High	Low	High	Low
Haas 2004	Low	Low	Low	Low	High	High	Low	High	Low
Mandelcorn 2004	Low	Unclear	Low	Low	Low	High	High	Low	Low
Pope 2004	Unclear	High	Low	Low	High	High	Low	Low	Low
Wegman 2003	Low	Low	Low	Low	High	High	Low	High	Low

Wolfe 2002	Low	Low	Low	Low	High	Low	Low	High	Low
Reitberg 2002	Low	Low	Low	Low	Low	High	Low	Low	Low
Linday 2001	Unclear	Low	Low	Low	Low	High	High	High	Low
Duggan 2000	Unclear	Unclear	Low	Low	High	High	High	Low	Low
Nikles 2000	Unclear	Unclear	Low	Low	High	High	High	High	Low
Mahon 1999	Low	Unclear	Low	Low	High	Low	High	High	Low
Bollert 1999	Unclear	Unclear	Low	Low	High	High	High	High	Low
Kent 1999	Unclear	Unclear	Low	Low	High	High	High	Low	Low
Webb 1999	Unclear	Unclear	Low	Low	Low	Low	High	High	Low
Haines 1999	Unclear	Unclear	Low	Low	Low	Low	Low	High	Low
Sheather-Reid 1998	Unclear	Unclear	Low	Low	High	High	Low	High	Low
Camfield 1996	Unclear	Unclear	Low	Low	High	High	High	Low	Low
Mahon 1996	Low	Unclear	Low	Low	High	High	High	Low	Low
Miyazaki 1995	Unclear	High	High	High	High	High	High	High	Low
Maier 1994	Unclear	Unclear	Low	Low	Low	Low	Low	High	Low
McQuay 1994	Low	Low	Low	Low	High	High	High	High	Low
March 1994	Unclear	Unclear	Low	Low	High	High	Low	High	Low
Denburg 1994	Unclear	Unclear	Low	Low	Low	Low	High	High	Low
Privitera 1994	Unclear	Unclear	Low	Low	High	High	High	Low	Low
Wallace 1994	High	Unclear	Low	Low	High	High	High	Low	Low
Langer 1993	Low	Low	Low	Low	High	High	High	Low	Low
Molloy 1993	Unclear	Unclear	Low	Low	Low	Low	Low	High	Low
Johannessen 1992	Unclear	Unclear	Low	Low	High	Low	High	High	Low
Johannessen 1991	Unclear	Unclear	Low	Low	High	High	Low	Low	Low
Patel 1991	Unclear	Unclear	Low	Low	High	High	High	Low	Low
Larsen 1991	Unclear	Unclear	Low	Low	High	High	High	High	Low
Jaeschke 1991	Unclear	Unclear	Low	Low	low	High	High	High	low
Hinderer 1990	Unclear	Unclear	Low	Low	low	High	high	low	low
Lashner 1990	Unclear	Low	Low	Low	Unclear	High	high	low	low

McBride 1988	Low	Low	Low	Low	Unclear	High	high	low	High
Menard 1988	Low	Unclear	Low	Low	Low	low	low	low	High
Ullmann 1986	Low	Unclear	Low	Low	Unclear	High	low	low	High
Parodi 1986	Low	Unclear	Low	Low	low	Low	low	low	low
Parodi 1979	Unclear	Unclear	Low	Low	low	High	High	low	low
Joy 2014	Low	Unclear	Low	Low	High	Low	low	low	low
Lipka 2017	Low	Low	Low	Low	High	Low	High	low	low
Mitchell 2015	Low	Low	Low	Low	High	Low	High	low	low
Nikles 2015	Low	Low	Low	Low	High	Low	High	low	low
Nikles 2017	Low	Low	Low	Low	High	Low	low	High	low
Nikles 2016	Low	Unclear	Low	Low	High	High	High	low	High
McGarry 2017	Low	Low	Low	Low	Low	Low	High	High	High

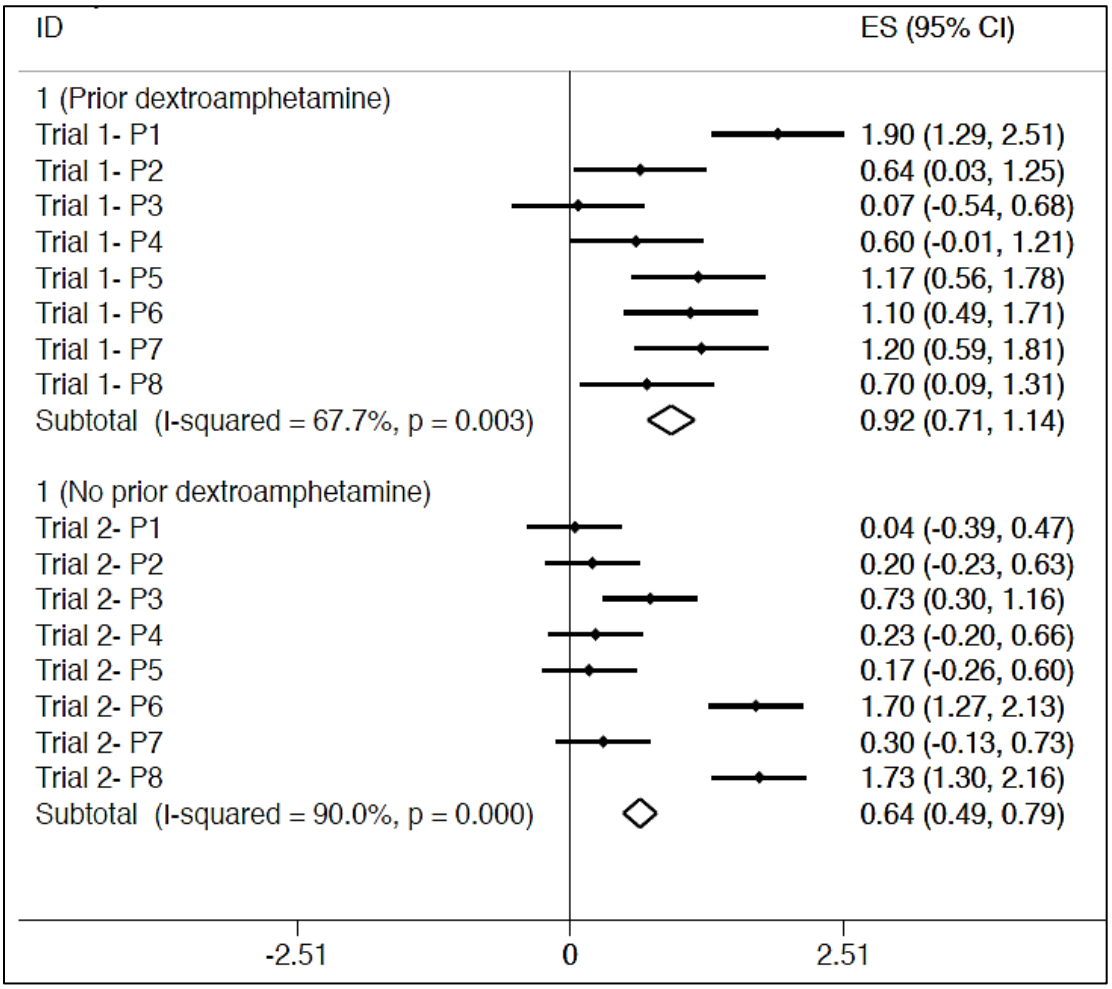
* Statistical methods used to account for carryover effect, period effects, and intra-subject correlation

Appendix Figure 1: Patients with chronic intestinal pseudo-obstruction treated with prucalopride or placebo for pain relief[1]



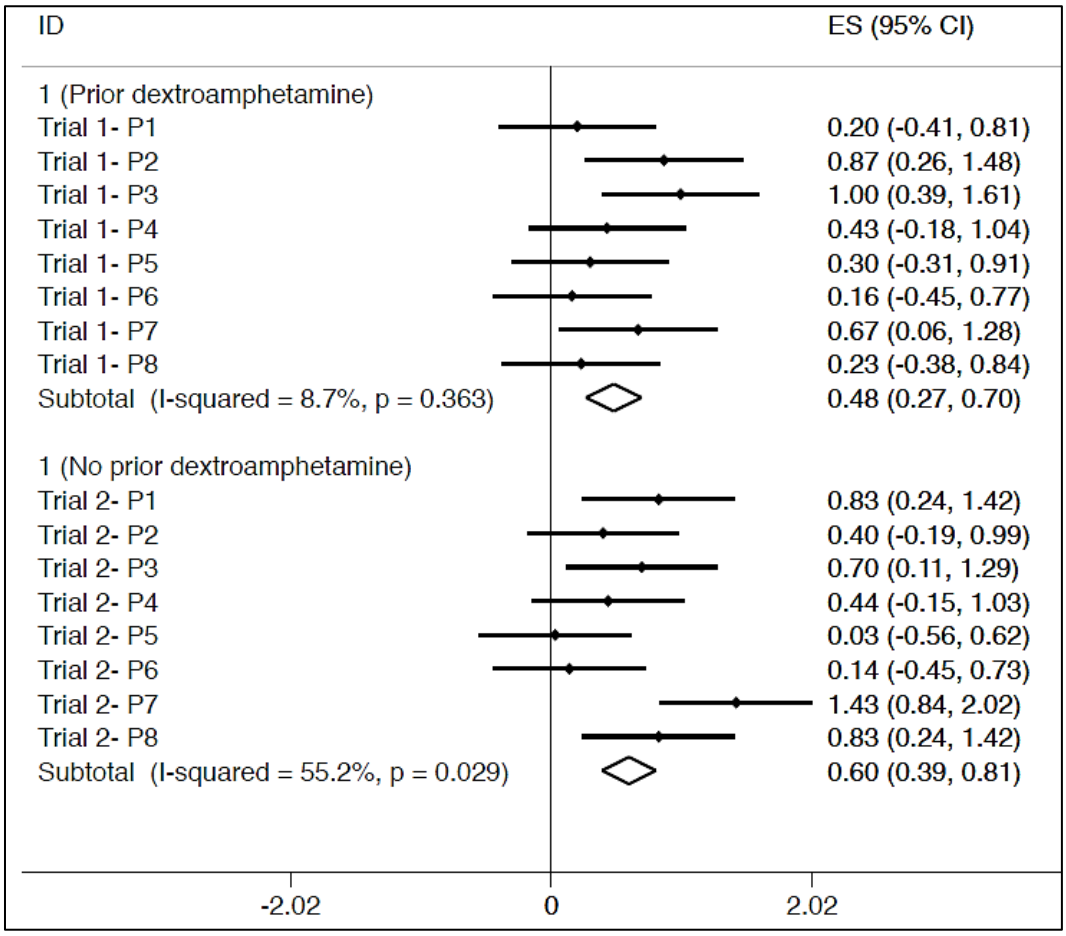
Appendix Figure 1 Legend:
Data from this figure was extracted from the study published by Emmanuel et al in 2011, which investigates the use of prucalopride or placebo for pain relief (among other outcomes) in patients with chronic intestinal pseudo-obstruction. The average treatment effect is -0.440 (-0.771 to -0.110).

Appendix Figure 2: Patients with chronic tension-type headaches treated with dextroamphetamine or control and effect on mean daily grade decrease in headache[2]



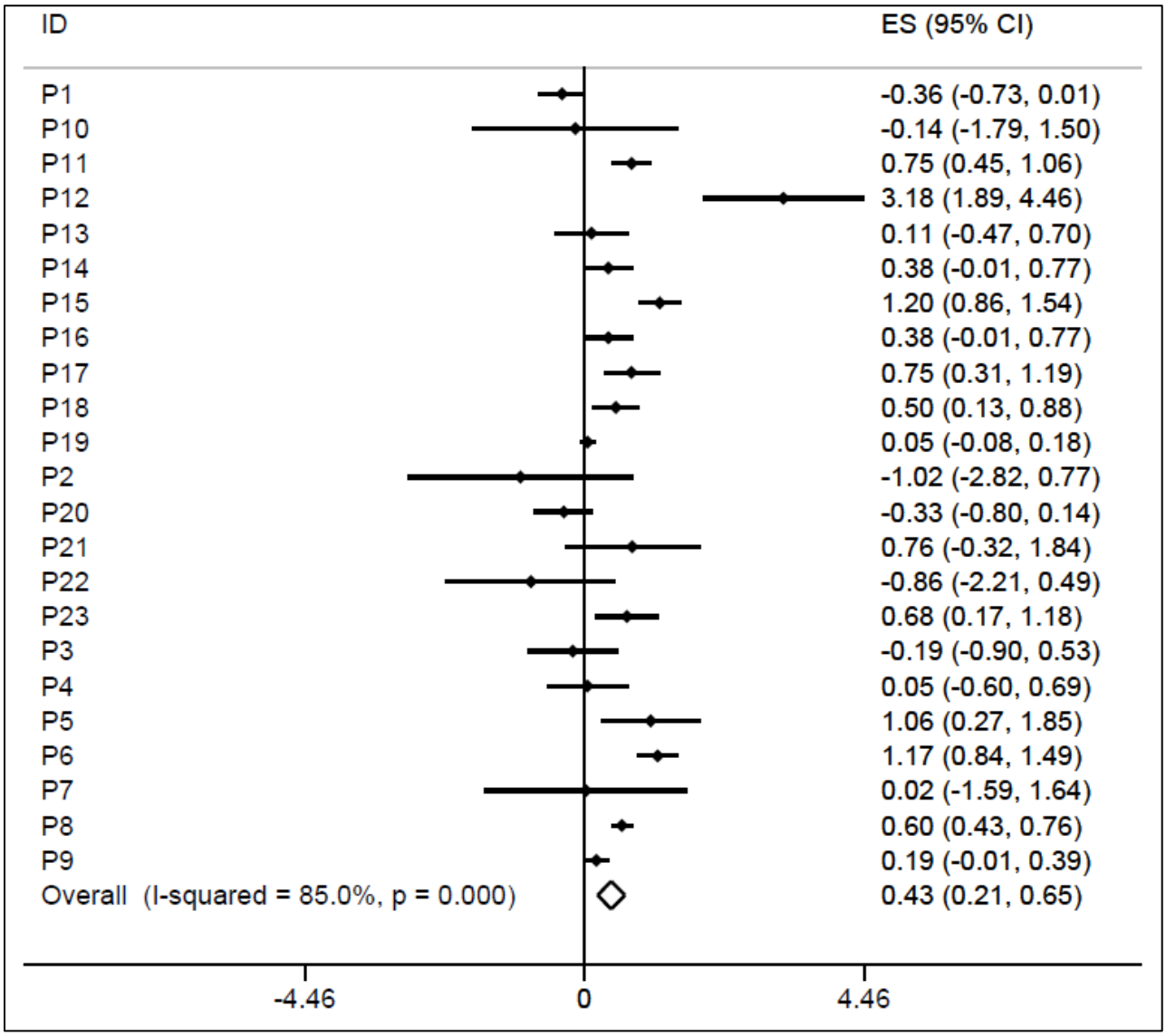
Appendix Figure 2 Legend: Data from this figure was extracted from the study published by Haas et al in 2004, which investigates the use of dextroamphetamine or control in patients with chronic-type for improvement on mean daily grade in headache.

Appendix Figure 3: Patients with migraine headaches treated with dextroamphetamine or control and effect on mean daily grade decrease in headache[2]



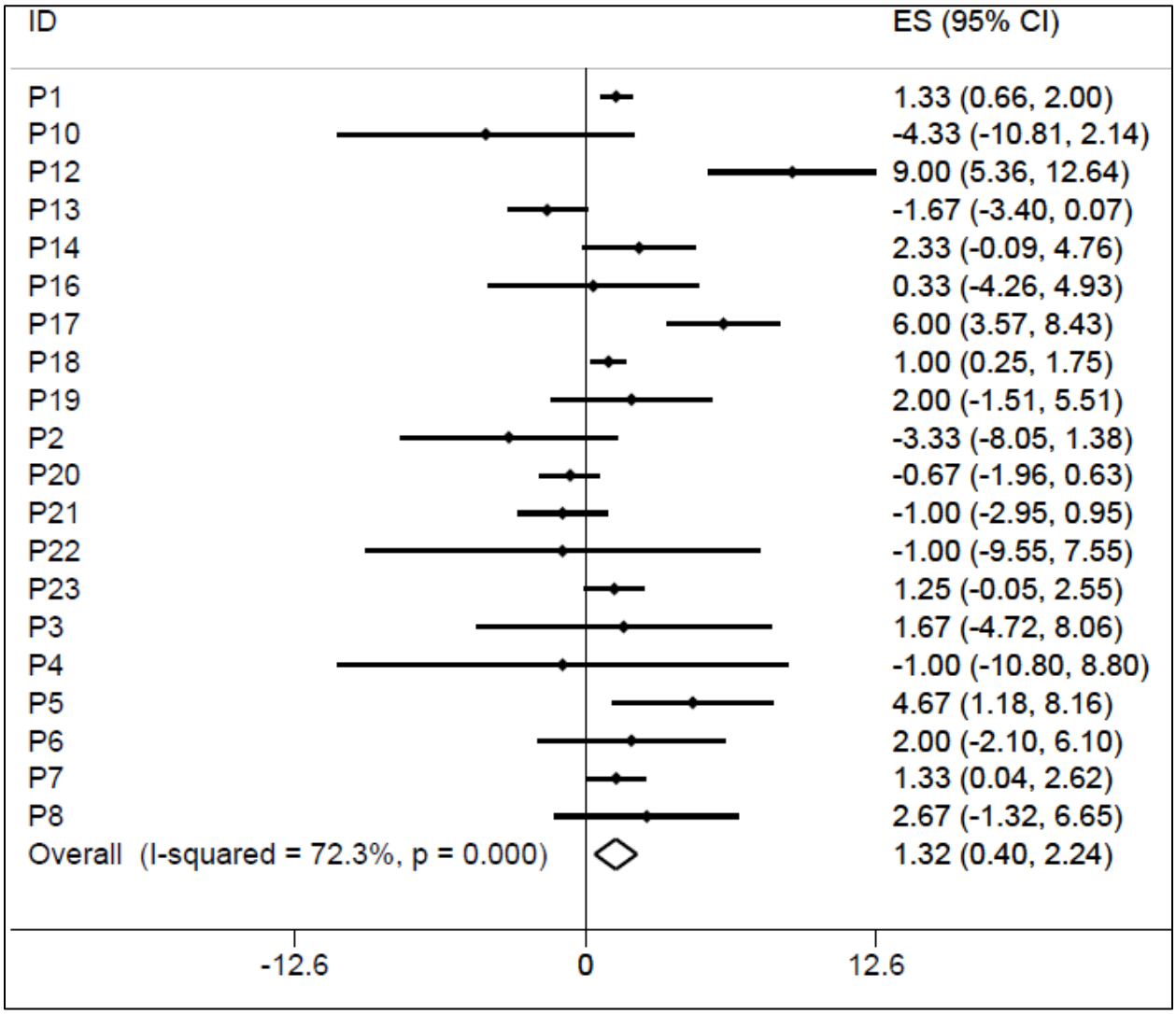
Appendix Figure 3 Legend: Data from this figure was extracted from the study published by Haas et al in 2004, which investigates the use of dextroamphetamine or control in patients with chronic-type and migraine headaches for improvement on mean daily grade in headache.

Appendix Figure 4: Patients with fibromyalgia treated with amitriptyline or placebo and its effect on a 7-point symptom scale[3]



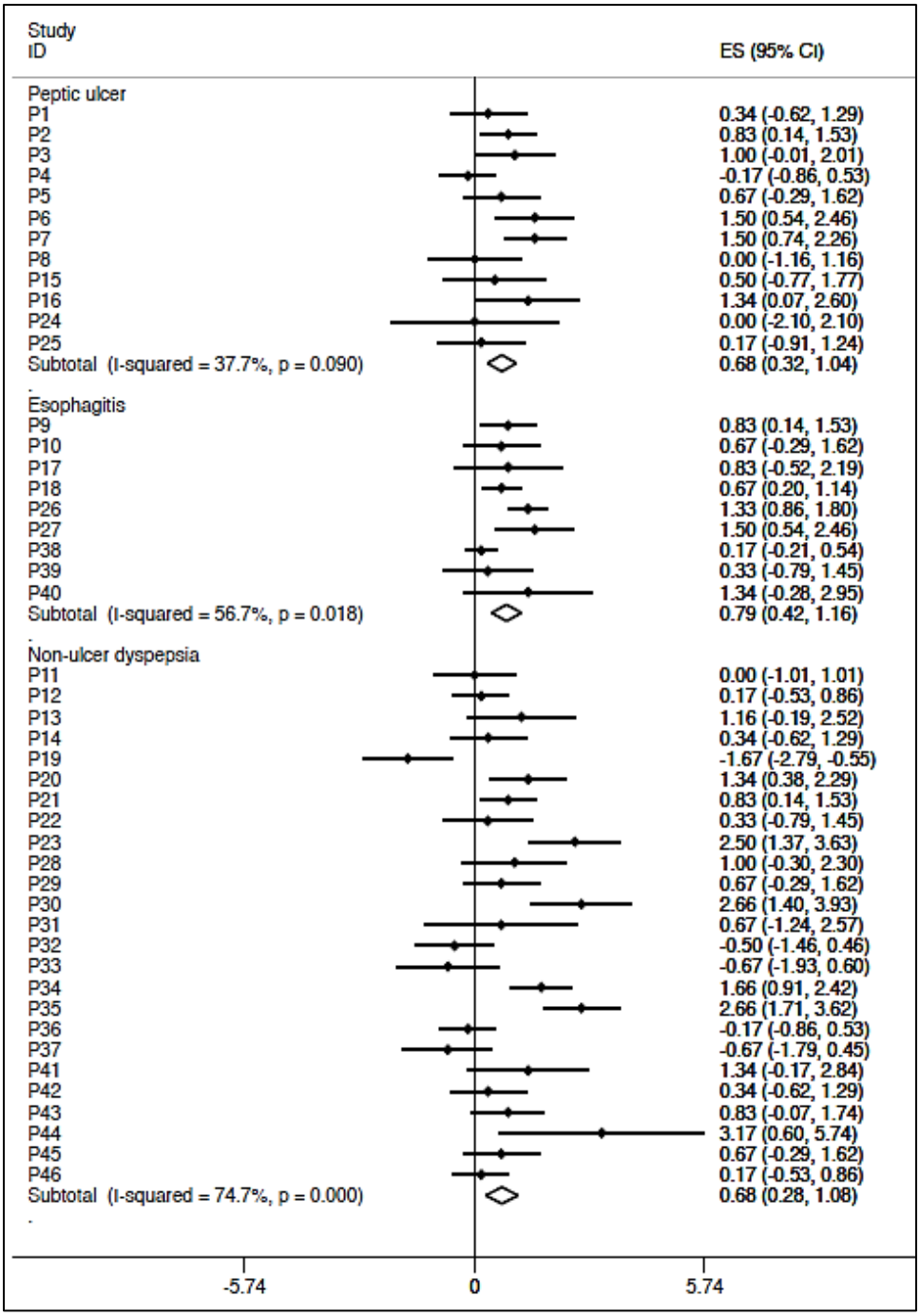
Appendix Figure 4 Legend: Data from this figure was extracted from the study published by Jaeschke et al in 1991, which investigates the effect of amitriptyline or placebo on a 7-point symptom scale in patients with fibromyalgia. The average treatment effect is 0.427 (0.210 to 0.645).

Appendix Figure 5: Patients with fibromyalgia treated with amitriptyline or placebo and its effect on tender point changes count[3]



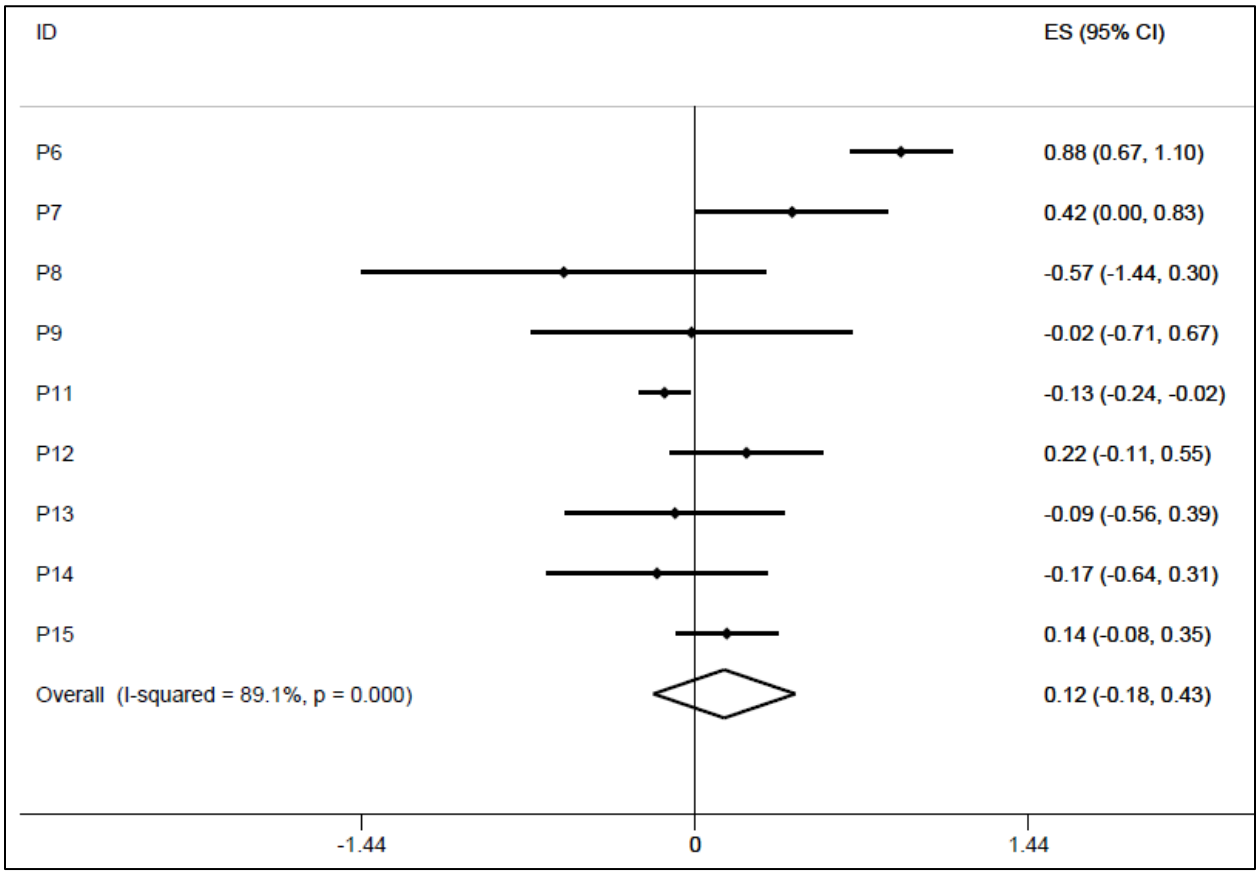
Appendix Figure 5 Legend: Data from this figure was extracted from the study published by Jaeschke et al in 1991, which investigates the effect of amitriptyline or placebo on tender point changes count in patients with fibromyalgia. The average treatment effect is 1.320 (0.404 to 2.236).

Appendix Figure 6: Patients with peptic ulcers, oesophagitis grade I, II, or III, or with reflux or ulcer-like symptom profiles were treated with cimetidine or placebo and its effect on a 6-point symptom scale[4]



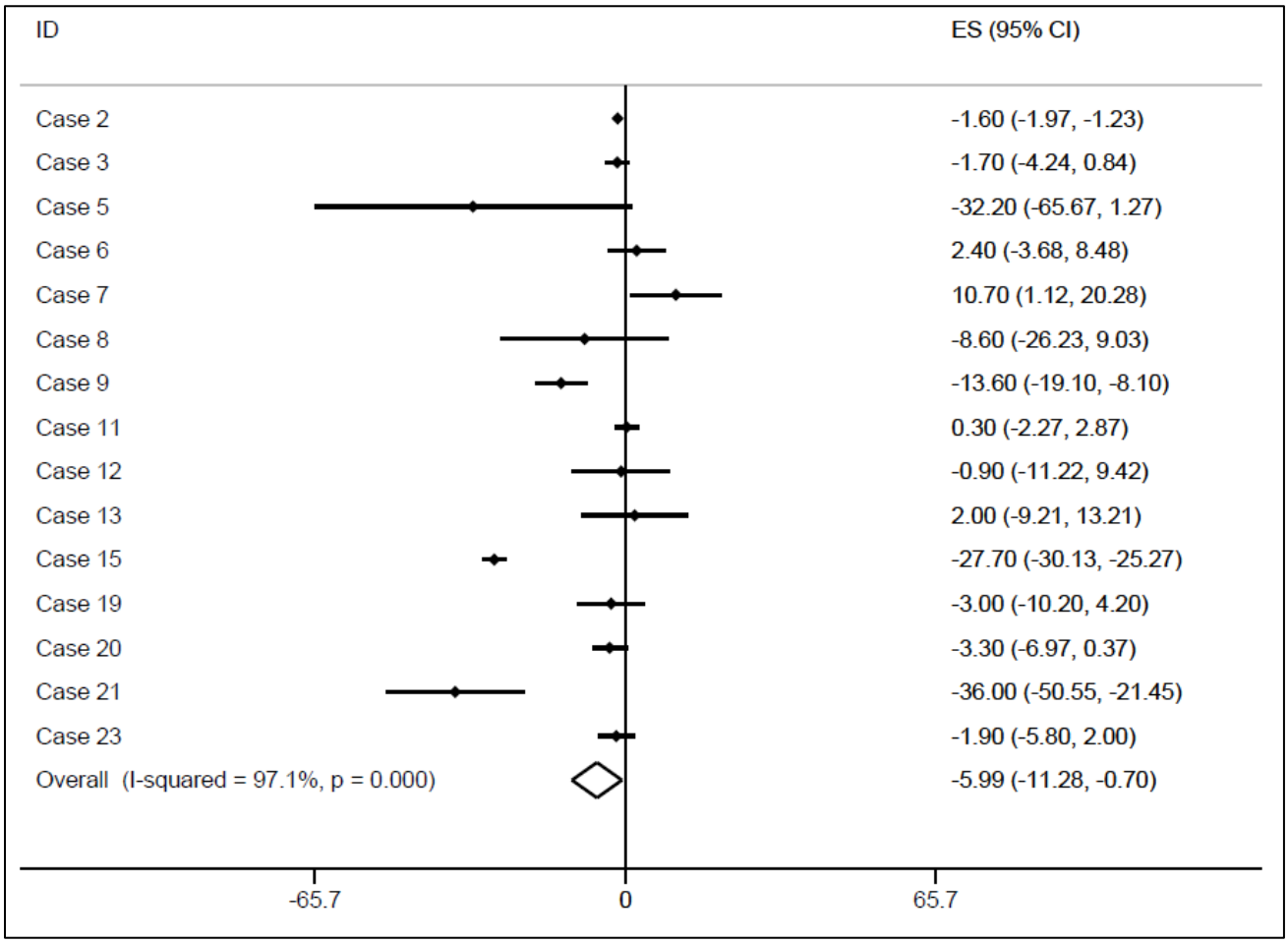
Appendix Figure 6 Legend: Data from this figure was extracted from the study published by Johannessen et al in 1992, which investigates the effect of cimetidine or placebo on a 6-point symptom scale in patients with peptic ulcers, oesophagitis grade I, II, or III, or with reflux or ulcer-like symptom profiles. The average treatment effect is 0.698 (0.466 to 0.931).

Appendix Figure 7: Patients with irreversible chronic airflow limitation treated with theophylline or placebo and its effect on dyspnea[5]



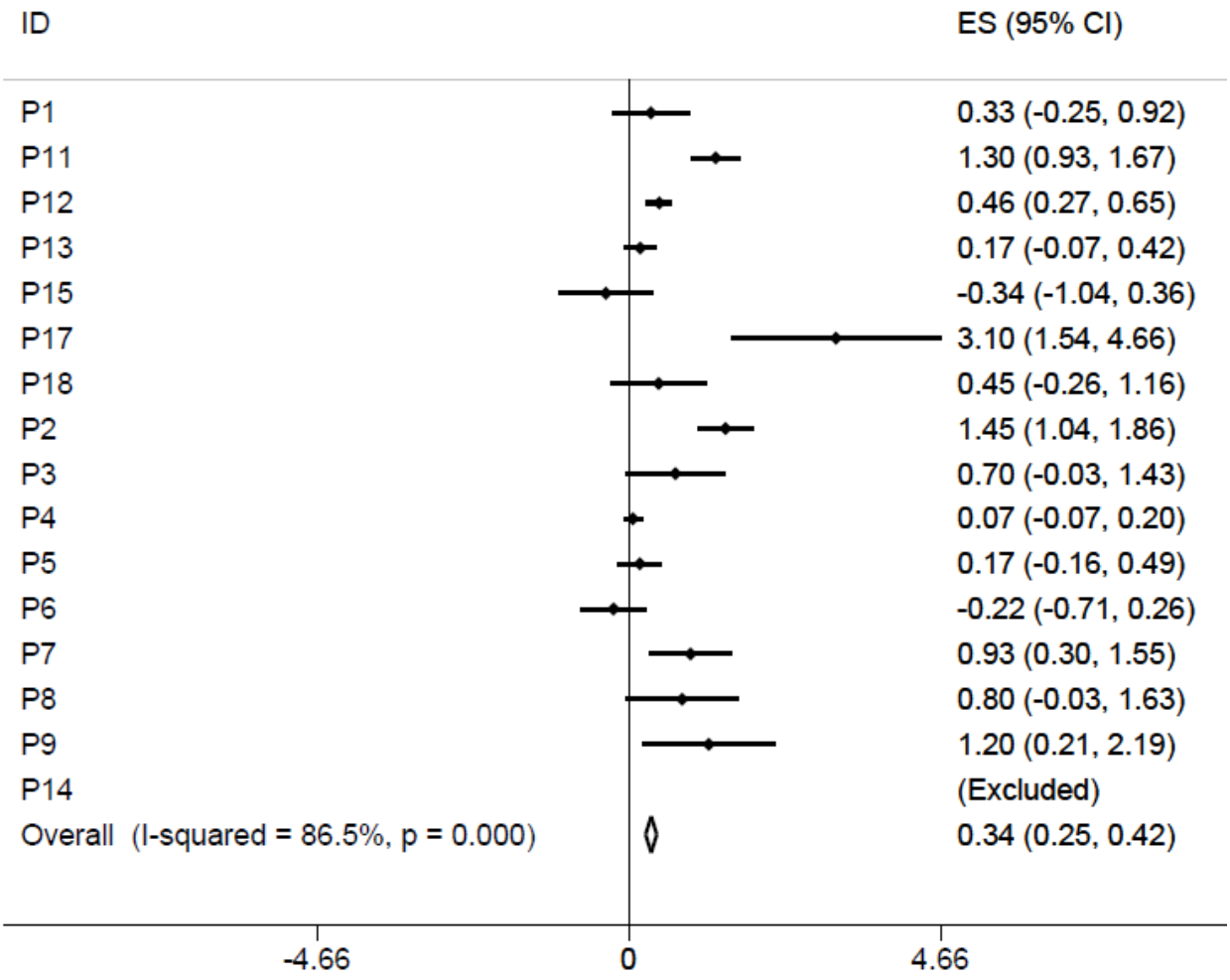
Appendix Figure 7 Legend: Data from this figure was extracted from the study published by Mahon et al in 1996, which investigates the effect of theophylline or placebo on dyspnea in patients with irreversible chronic airflow limitation. The average treatment effect is 0.125 (-0.181 to 0.430).

Appendix Figure 8: Patients with osteoarthritic pain treated with paracetmol and diclofenac and its effect on stiffness[6]



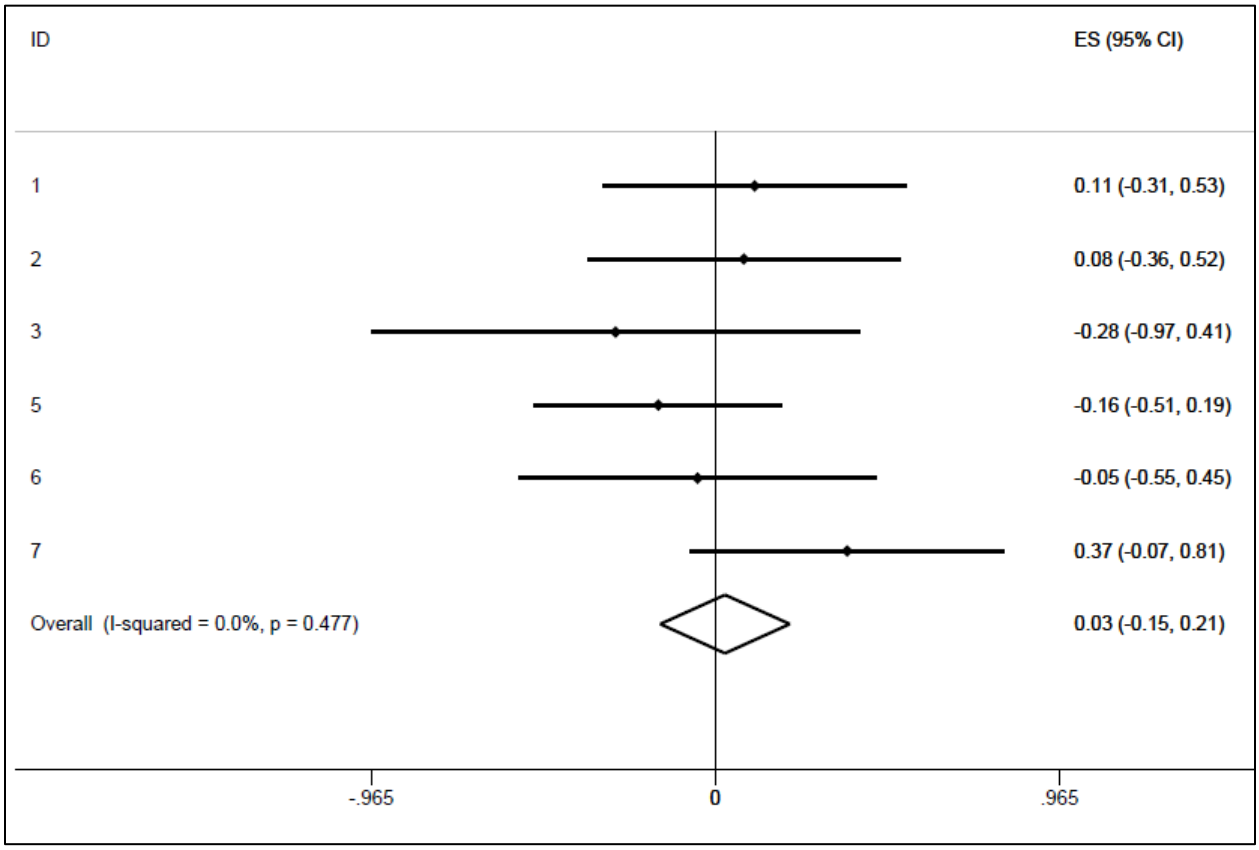
Appendix Figure 8 Legend: Data from this figure was extracted from the study published by March et al in 1994, which investigates the effect of paracetmol and diclofenac on stiffness in patients with osteoarthritic pain. The average treatment effect is mean difference in stiffness (mm).

Appendix Figure 9: Patients with nonreversible chronic airflow limitation treated with either ipratropium bromide, theophylline, salbutamol, or beclomethane (all compared to placebo) and its effect on a 4-item symptom questionnaire[7]



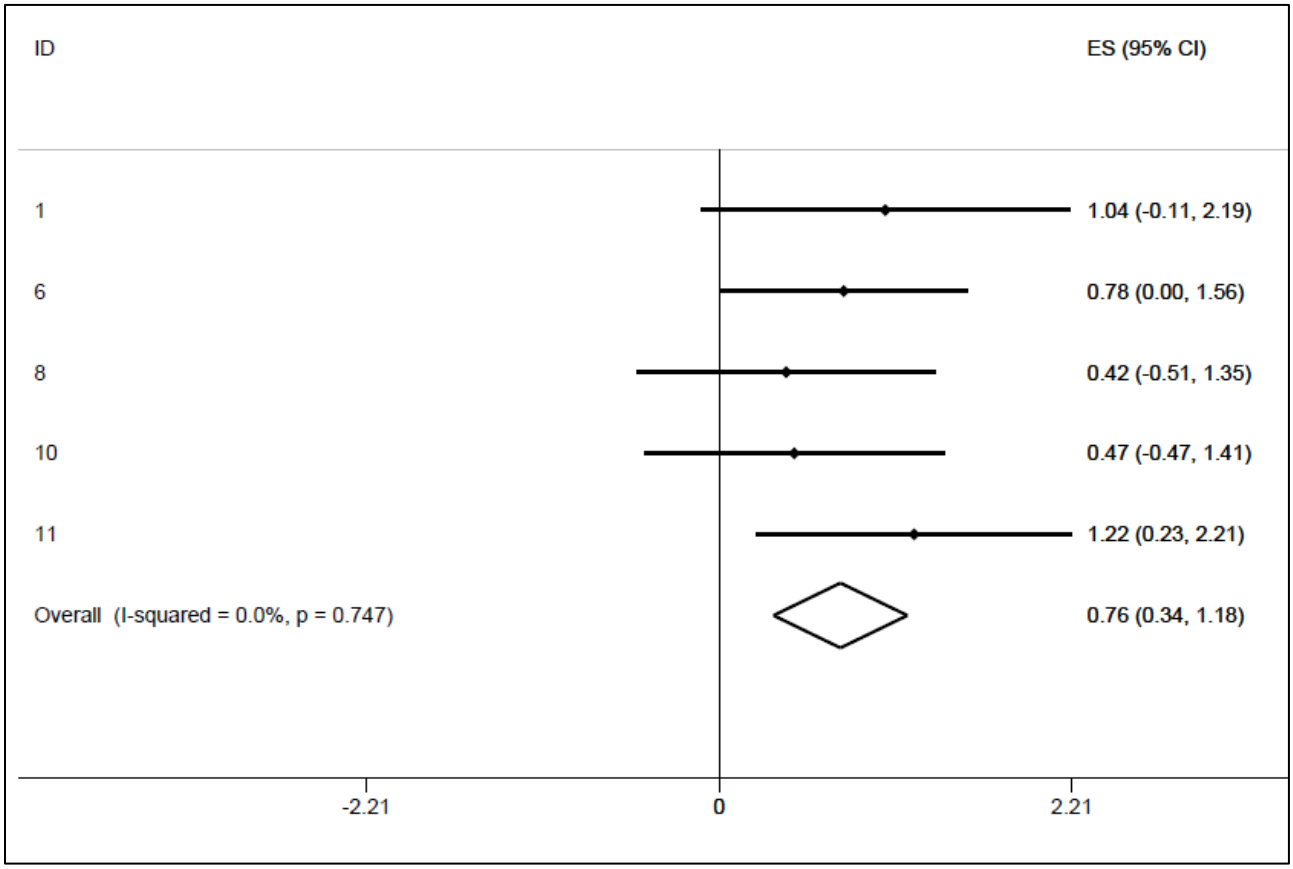
Appendix Figure 9 Legend: Data from this figure was extracted from the study published by Patel et al in 1991, which investigates the effect of ipratropium bromide, theophylline, salbutamol, or beclomethane (all compared to placebo) on a 4-item symptom questionnaire in patients with nonreversible chronic airflow limitation. The average treatment effect is 0.340 (0.253 to 0.422).

Appendix Figure 10: Patients previously taking warfarin for either atrial fibrillation or deep vein thrombosis treated with apo-warfarin and 20coumadin and its effect on international normalized ratio[8]



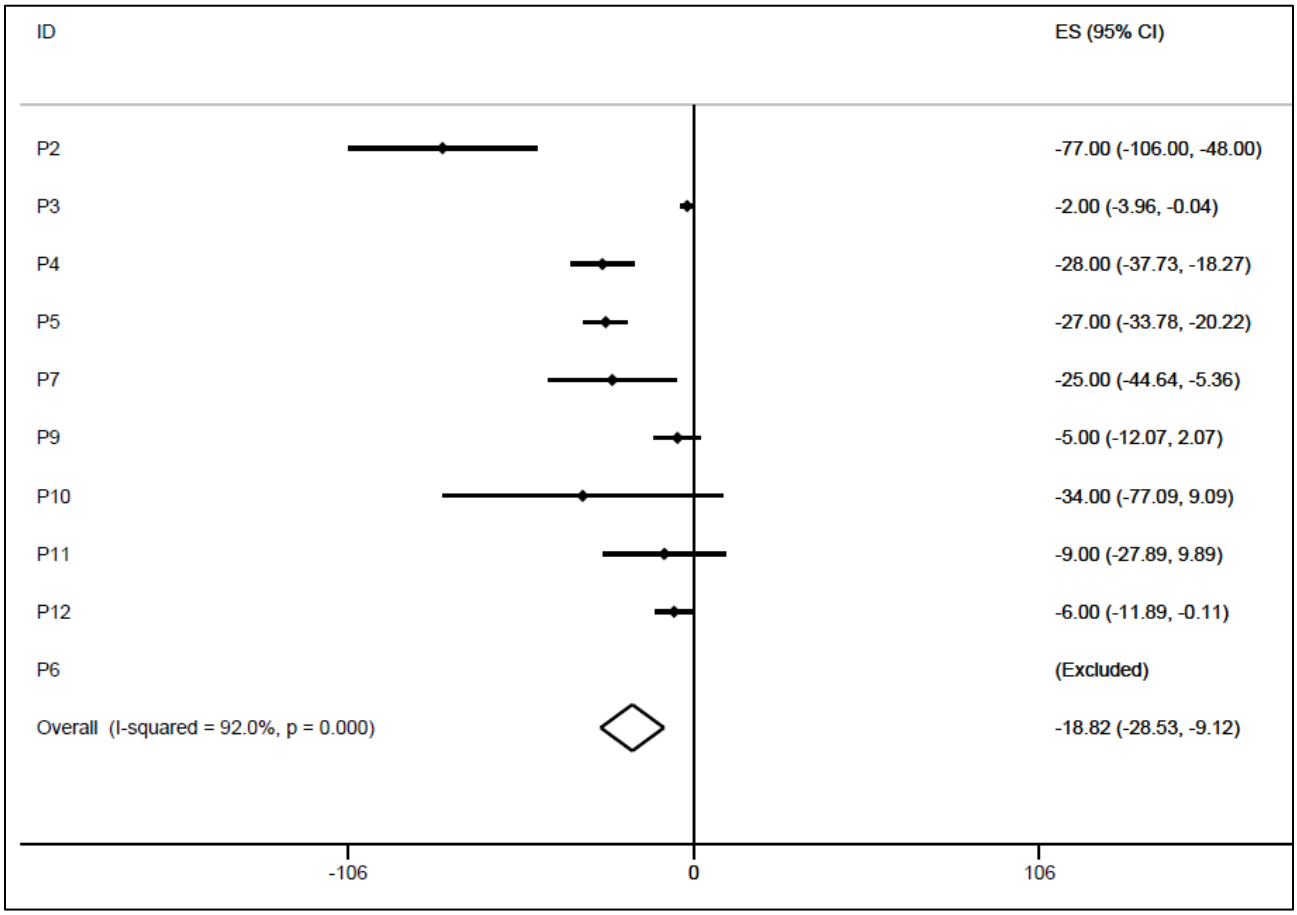
Appendix Figure 10 Legend: Data from this figure was extracted from the study published by Pereira et al in 1995, which investigates the effect of apo-warfarin and Coumadin on international normalized ratio in patients previously taking warfarin for either atrial fibrillation or deep vein thrombosis. The average treatment effect is 0.027 (-0.155 to 0.209).

Appendix Figure 11: Hospitalized children and adolescents with attention-deficit hyperactivity disorder treated with methylphenidate and placebo and its effect on Conners 15-item rating scale scores[9]



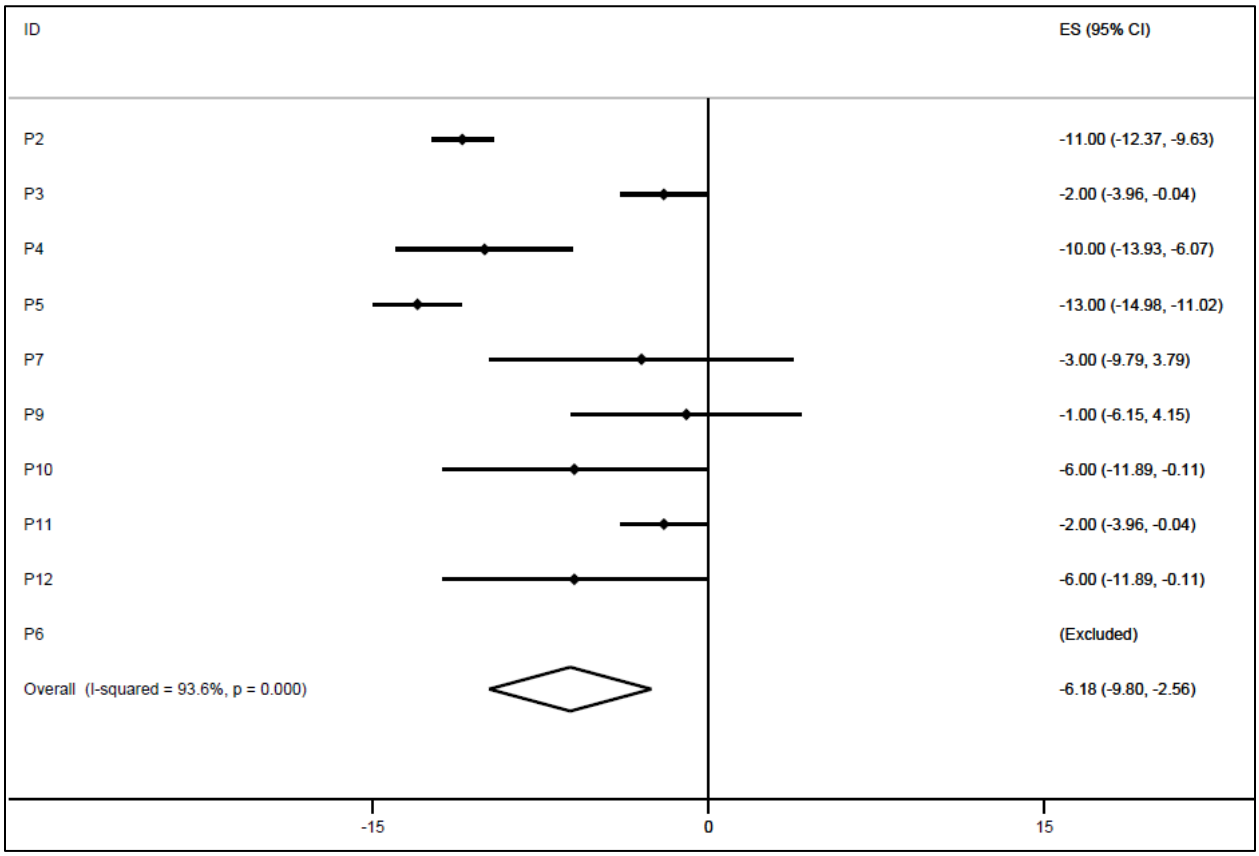
Appendix Figure 11 Legend: Data from this figure was extracted from the study published by Wallace et al in 1994, which investigates the effect of methylphenidate and placebo on Conners 15-item rating scale scores in hospitalized children and adolescents with attention-deficit hyperactivity disorder. The average treatment effect is 0.759 (0.341 to 1.178).

Appendix Figure 12: Patients already prescribed quinine treated with quinine sulphate and placebo, and its effect on changes in number of cramps[10]



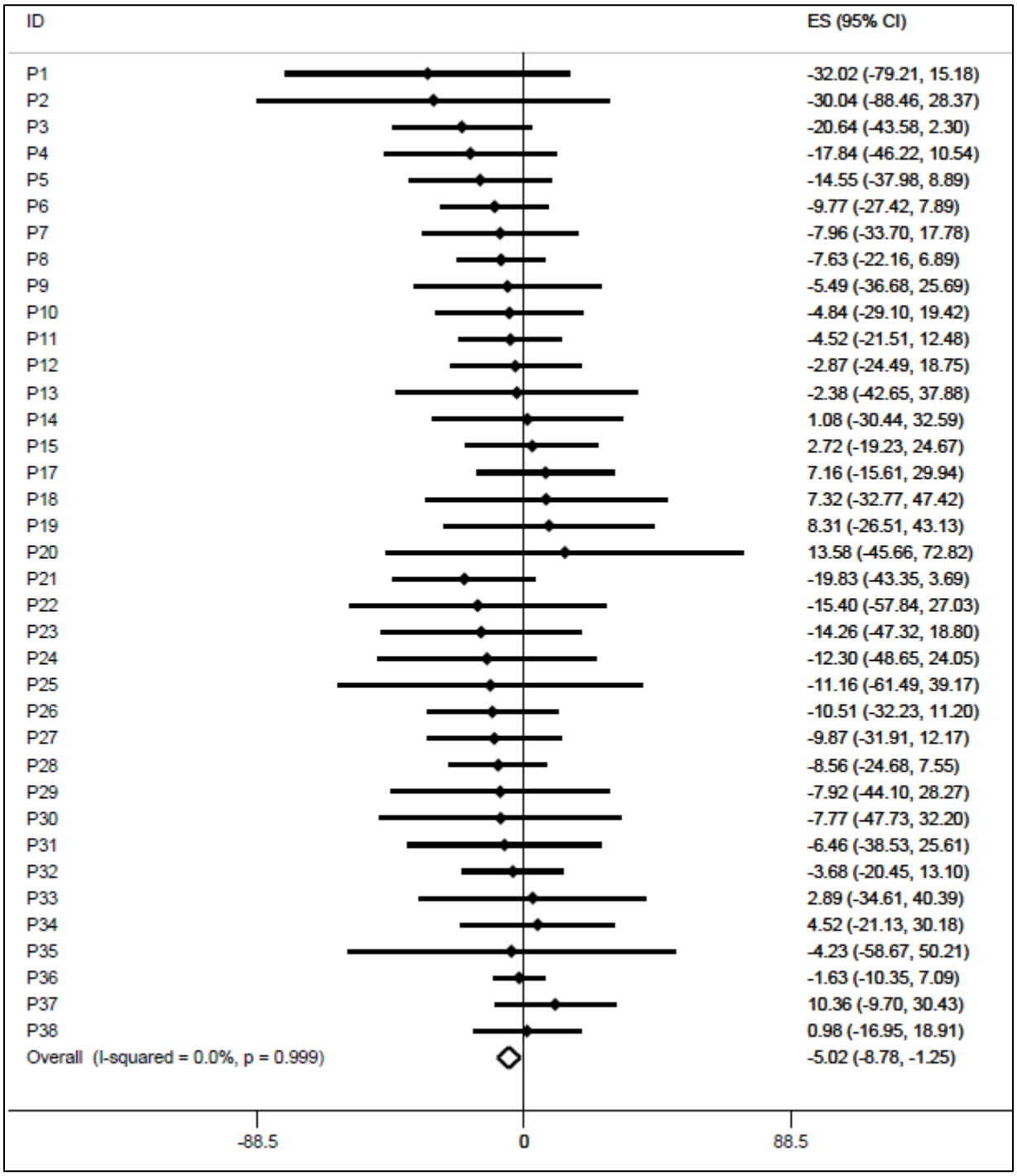
Appendix Figure 12 Legend: Data from this figure was extracted from the study published by Woodfield et al in 2005, which investigates the effect of quinine sulphate and placebo on changes in number of cramps in patients already prescribed quinine. The average treatment effect is -18.823 (-28.527 to -9.120).

Appendix Figure 13: Patients already prescribed quinine treated with quinine sulphate and placebo, and its effect on total days with cramps[10]



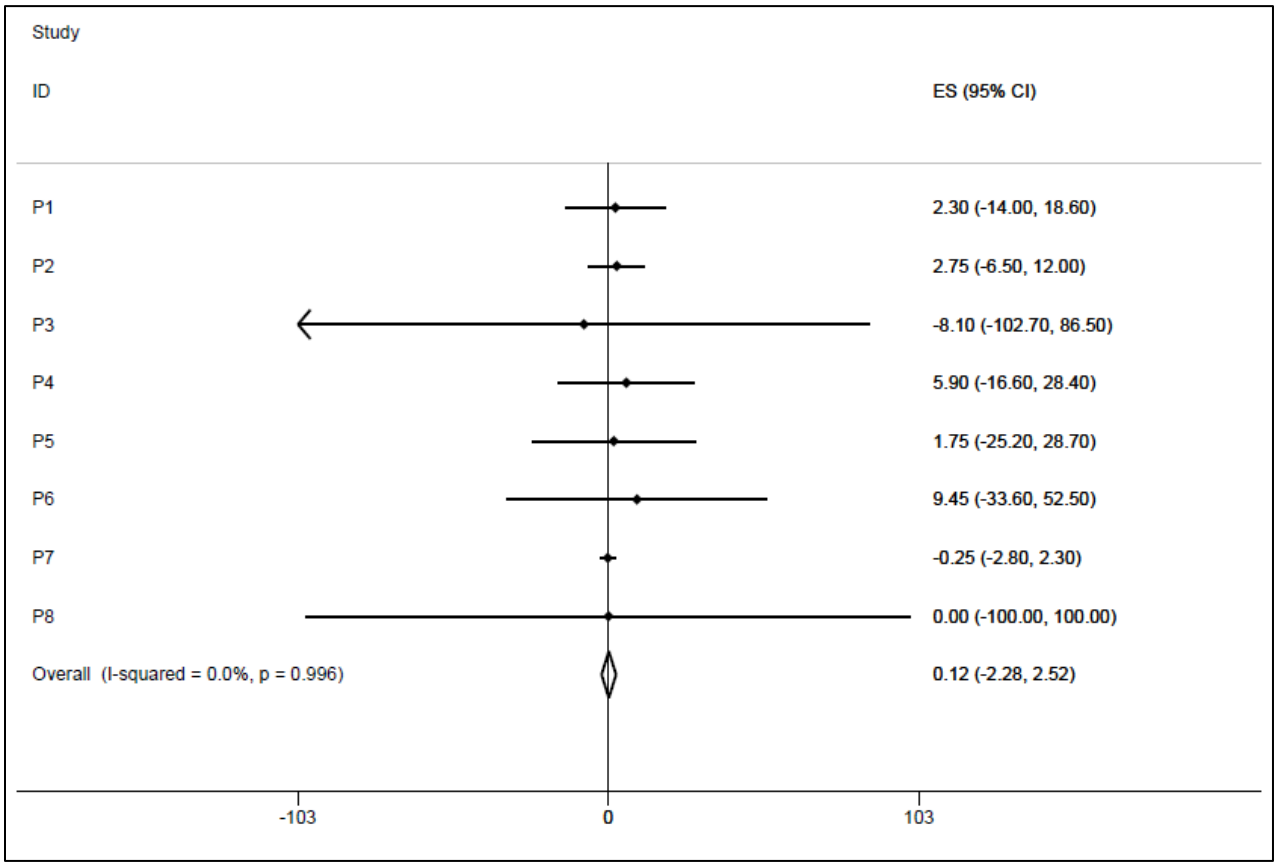
Appendix Figure 13 Legend: Data from this figure was extracted from the study published by Woodfield et al in 2005, which investigates the effect of quinine sulphate and placebo on total days with cramps in patients already prescribed quinine. The average treatment effect is -6.181 (-9.798 to -2.563).

Appendix Figure 14: Patients with fibromyalgia syndrome treated with amitriptyline and the combination amitriptyline and fluoxetine and its effect on the Fibromyalgia Impact Questionnaire[11]



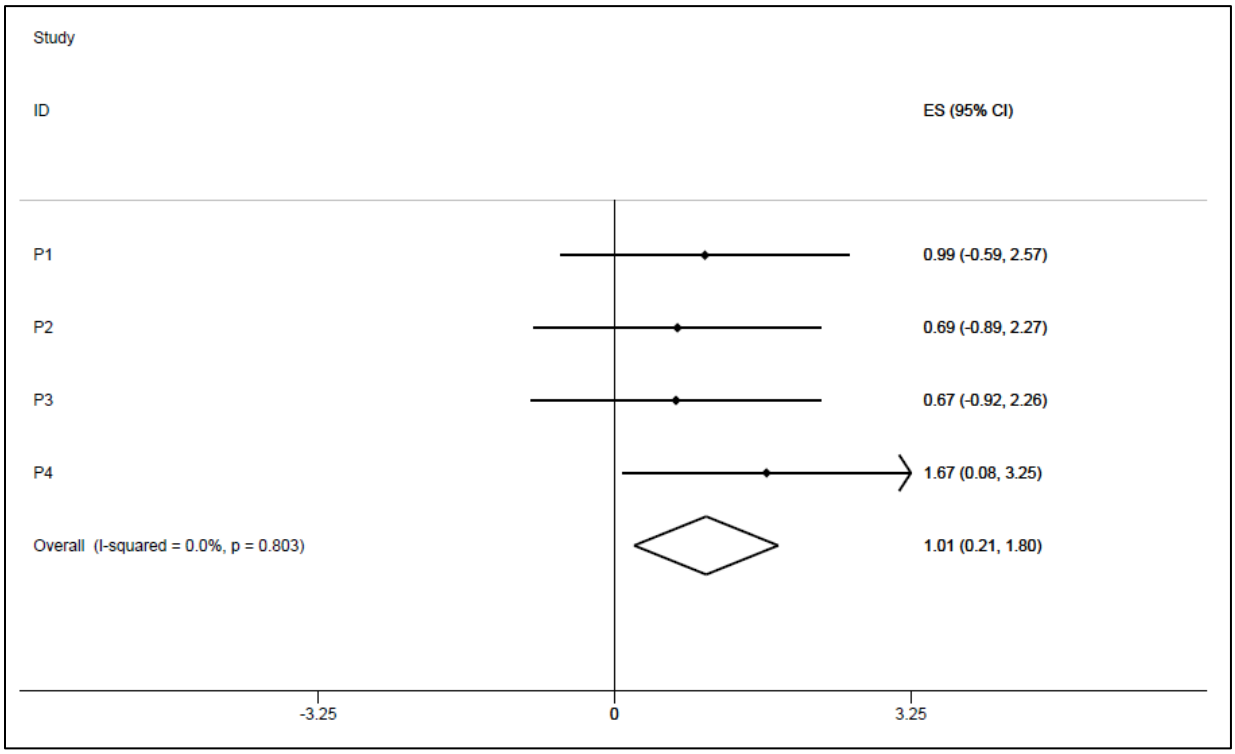
Appendix Figure 14 Legend: Data from this figure was extracted from the study published by Zucker et al in 2006, which investigates the effect of amitriptyline and the combination amitriptyline and fluoxetine on Fibromyalgia Impact Questionnaire in patients with fibromyalgia syndrome. The average treatment effect is -5.019 (-8.784 to -1.254).

Appendix 15: Patients with prior statin-related myalgia with or without mild elevation of creatine kinase levels treated with statin and placebo and its effects on VAS myalgia score[12]



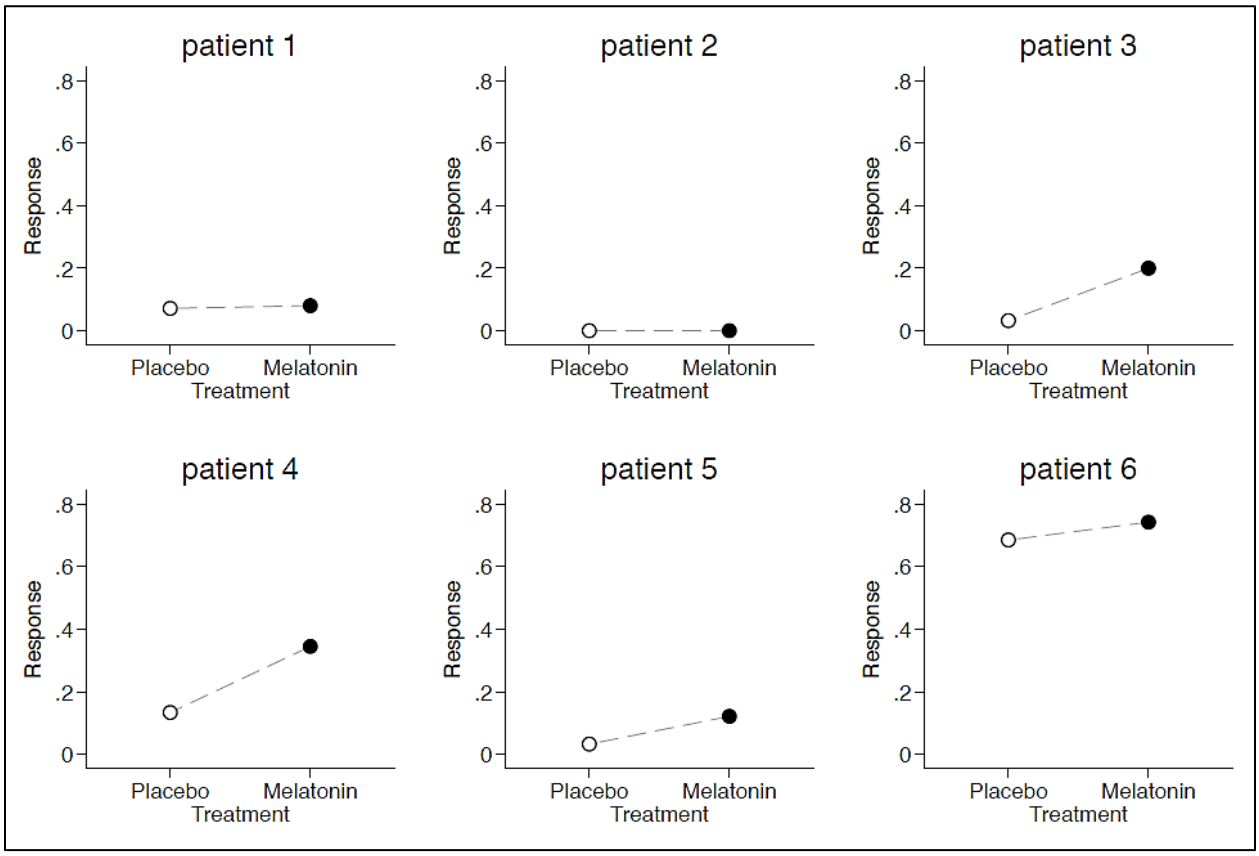
Appendix 15 Figure Legend: Data from this figure was extracted from the study published by Joy et al in 2014, which investigates the effect of statin versus placebo on VAS myalgia score in patients with hyperlipidemia. The average treatment effect is 0.12 (-2.28 to 2.52).

Appendix Figure 16: Patients with myasthenia gravis with acetylcholine receptor antibodies treated with ephinpherin and placebo and its effect on QMG score[13]



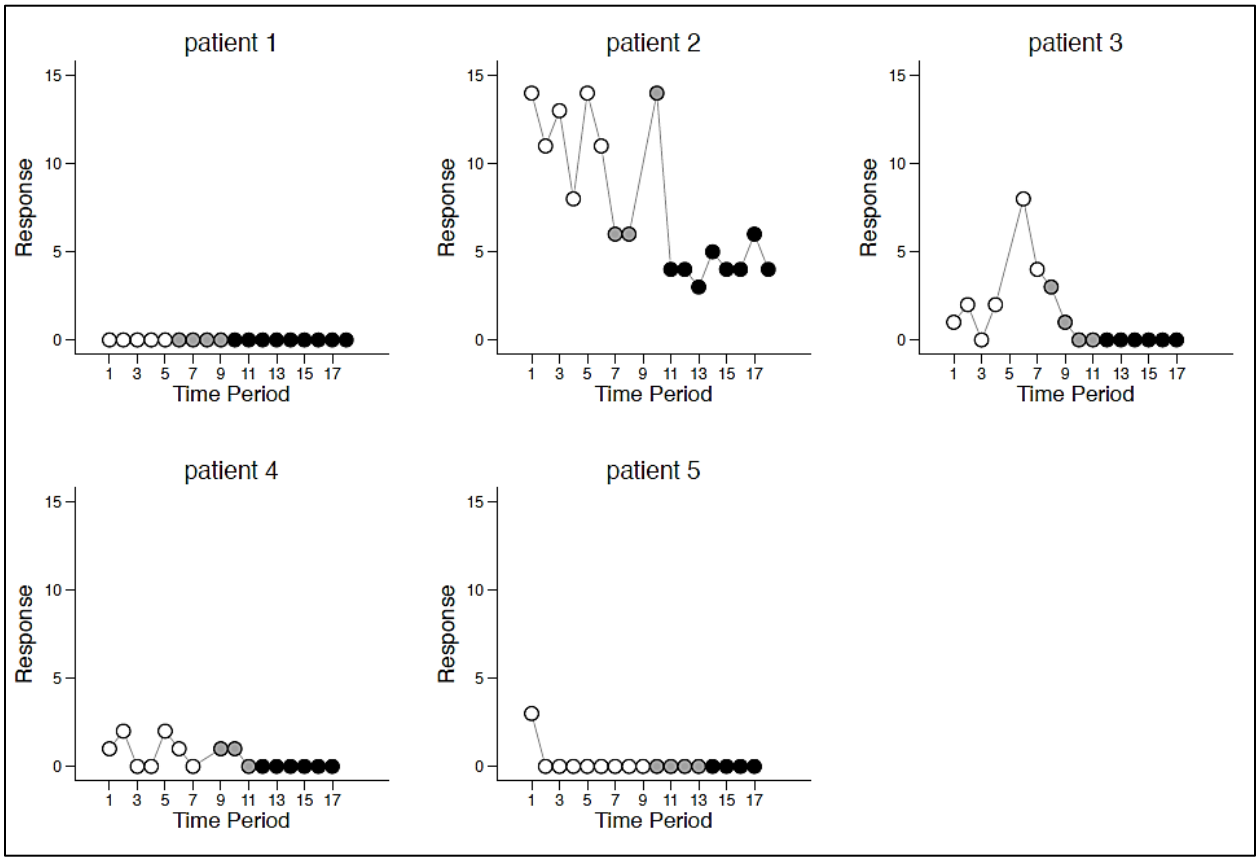
Appendix Figure 16 Legend: Data from this figure was extracted from the study published by Lipkin et al in 2017, which investigates the effect of with ephinpherin and placebo and its effect on QMG score in patients with autoimmune myasthenia gravia. The average treatment effect is 1.01 (0.21 to 1.80).

Appendix Figure 17: Children with mental retardation and fragmented sleep treated with melatonin and placebo and its effect on nights without awakening[14]



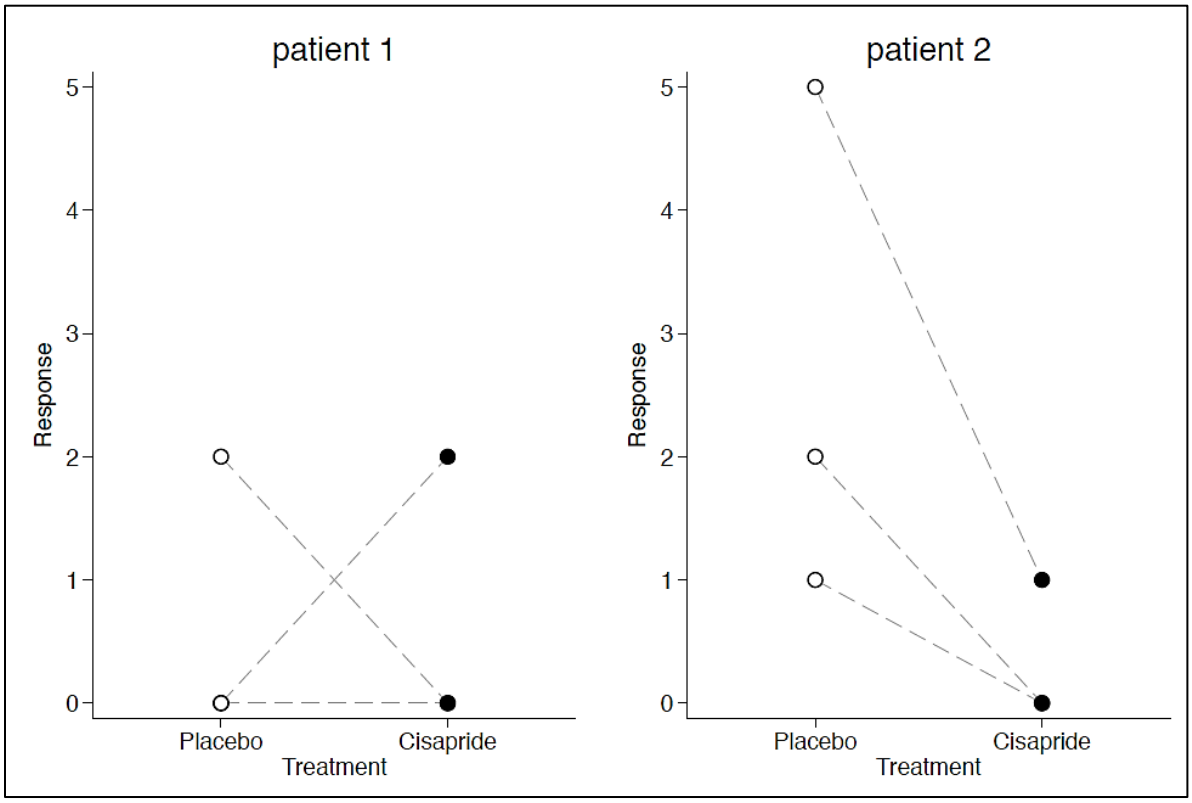
Appendix Figure 17 Legend: Data from this figure was extracted from the study published by Camfield et al in 1996, which investigates the effect of melatonin and placebo on nights without awakening in children with mental retardation and fragmented sleep. The average treatment effect is 0.84 (0.20 to 1.48). White circles indicate placebo; black circles indicate melatonin.

Appendix Figure 18: Patients with traumatic spinal cord lesions treated with baclofen and placebo and its effect on anxiety[15]



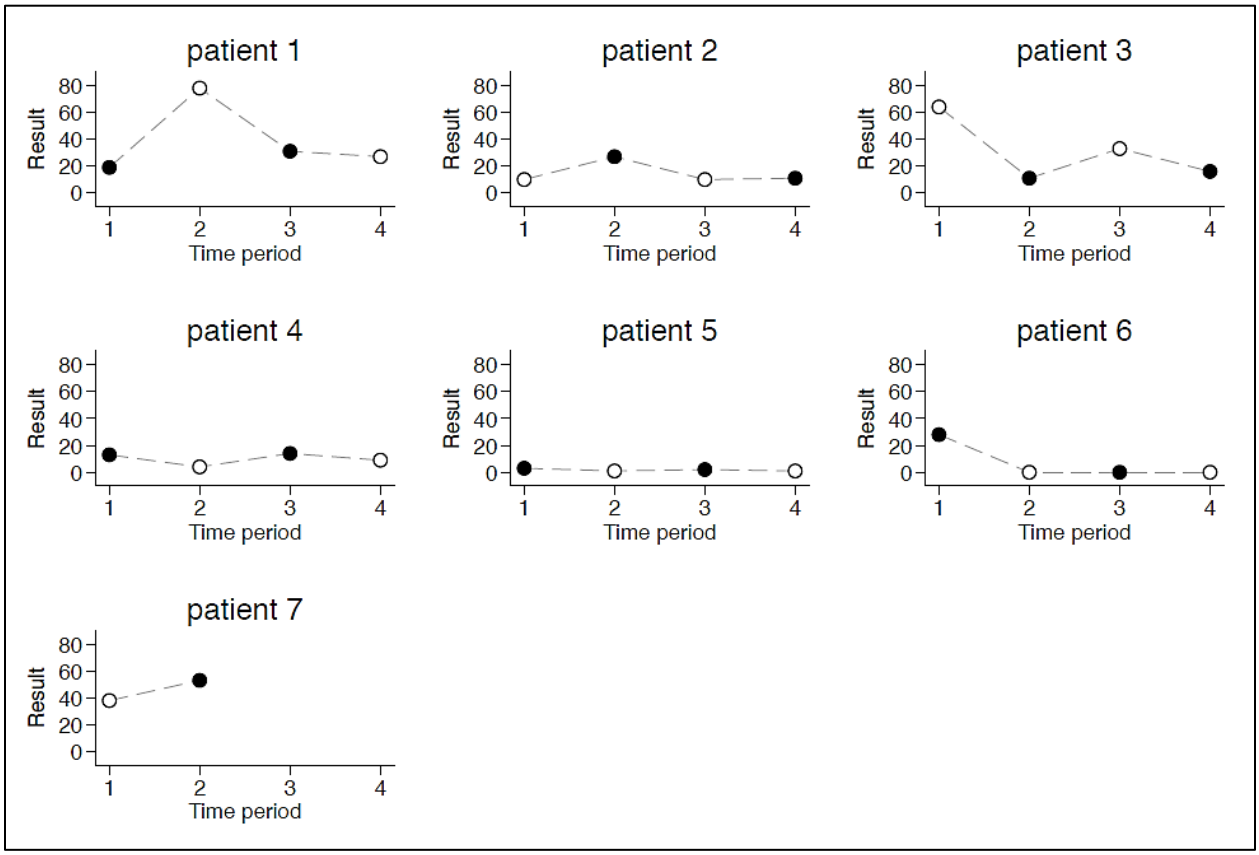
Appendix Figure 18 Legend: Data from this figure was extracted from the study published by Hinderer et al in 1990, which investigates the effect of baclofen and placebo on anxiety in patients with traumatic spinal cord lesions. The average treatment effect is -1.06 (-1.88 to -0.23). White circles indicate placebo; grey circles indicate a half dose (40 mg/day) of baclofen; black circles indicate a full dose (80 mg/day) of baclofen.

Appendix Figure 19: Children with gastroesophageal reflux treated with cisapride and placebo and its effect on emetic episodes per day[16]



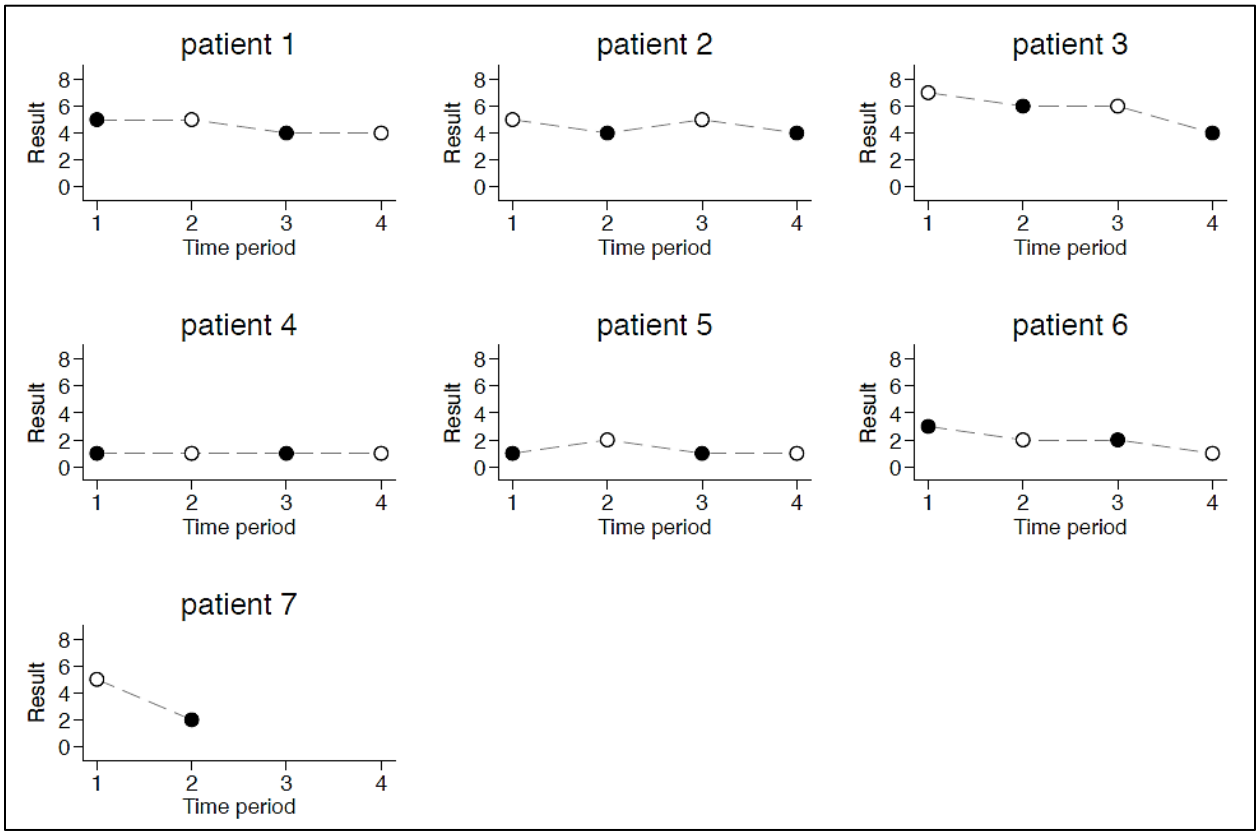
Appendix Figure 19 Legend: Data from this figure was extracted from the study published by Langer et al in 1993, which investigates the effect of cisapride and placebo on emetic episodes per day in children with gastroesophageal reflux. The average treatment effect is -1.20 (-2.49 to 0.09). White circles indicate placebo; black circles indicate cisapride.

Appendix Figure 20: Nonsmokers with ulcerative colitis treated with nicotine gum and placebo and its effect on abdominal pain[17]



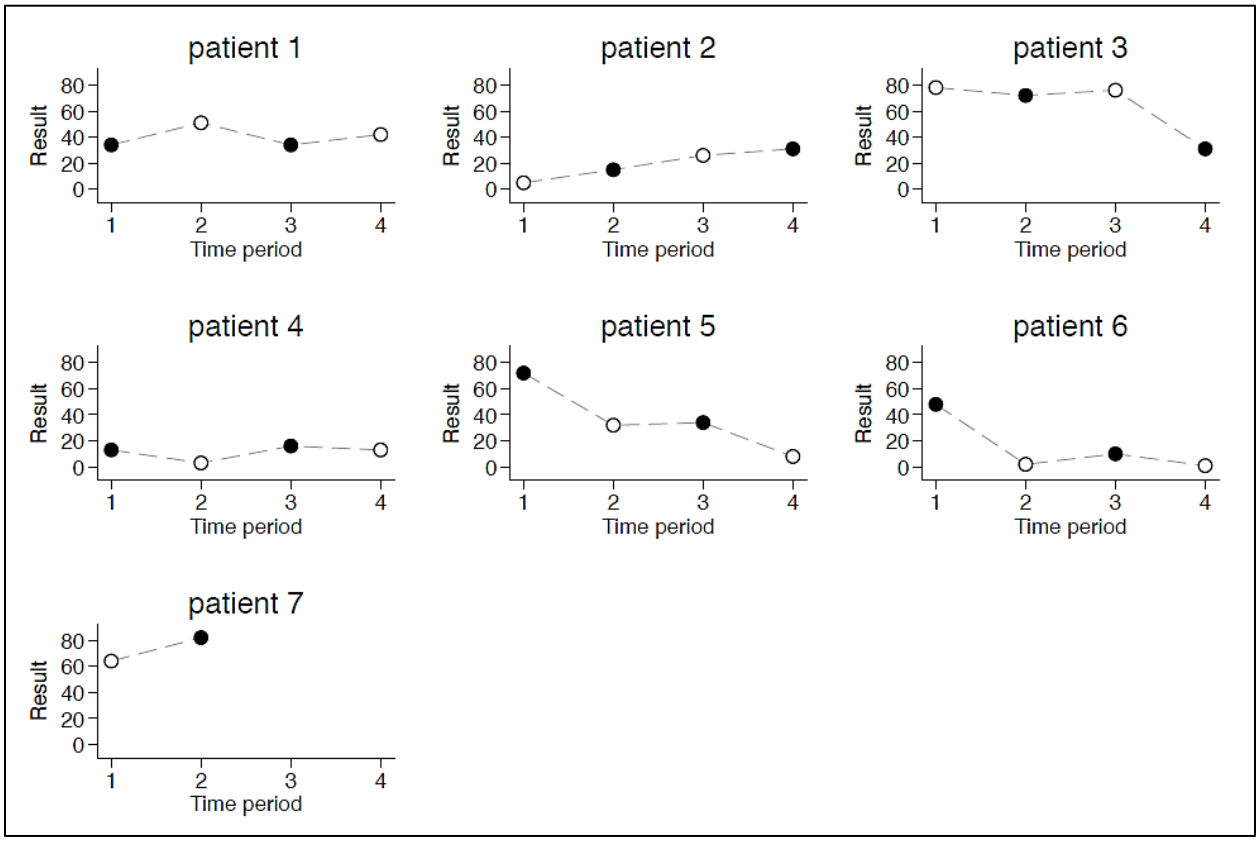
Appendix Figure 20 Legend: Data from this figure was extracted from the study published by Lashner et al in 1990, which investigates the effect of nicotine gum and placebo on abdominal pain in nonsmokers with ulcerative colitis. The average treatment effect is -3.62 (-15.84 to 8.61). White circles indicate placebo gum; black circles indicate nicotine gum.

Appendix Figure 21: Nonsmokers with ulcerative colitis treated with nicotine gum and placebo and its effect on bowel movements per day[17]



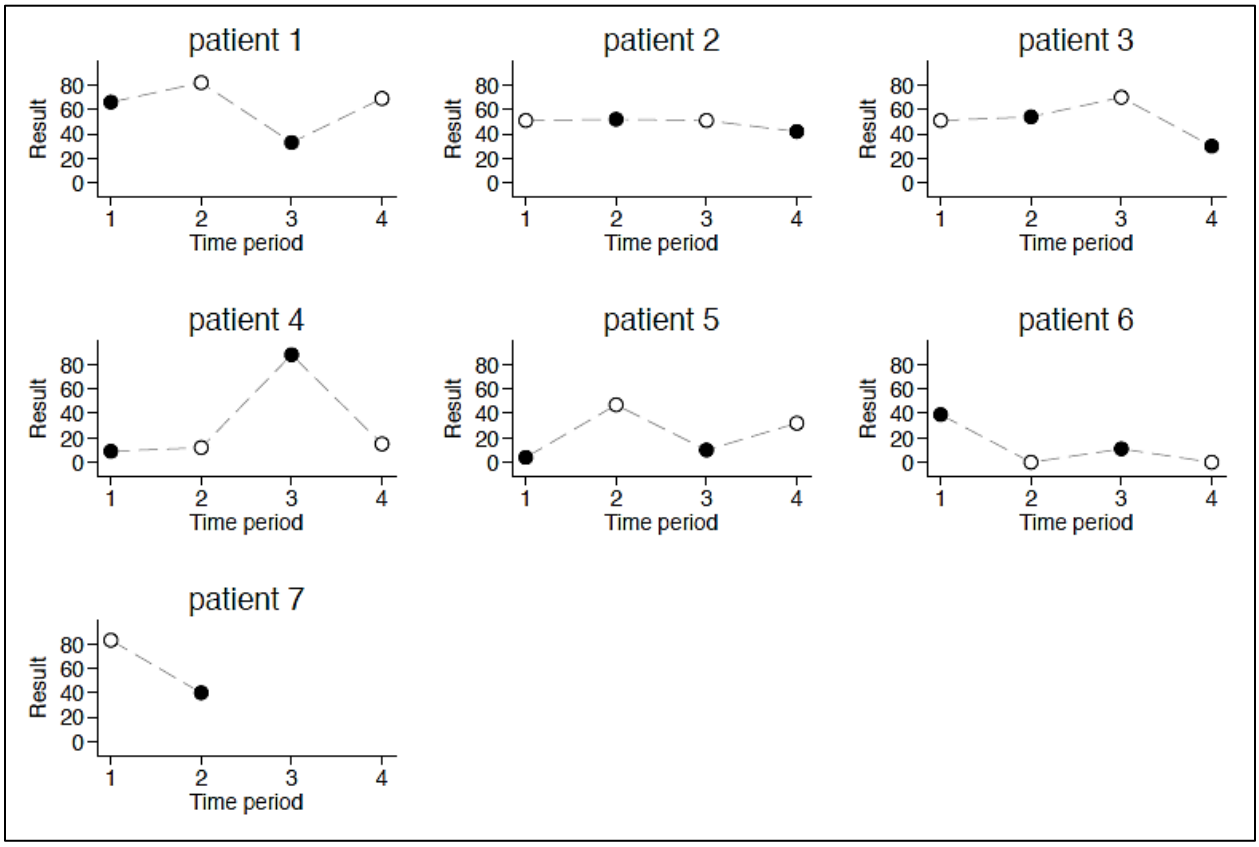
Appendix Figure 21 Legend: Data from this figure was extracted from the study published by Lashner et al in 1990, which investigates the effect of nicotine gum and placebo on bowel movements per day in nonsmokers with ulcerative colitis. The average treatment effect is -0.56 (-1.22 to 0.09). White circles indicate placebo gum; black circles indicate nicotine gum.

Appendix Figure 22: Nonsmokers with ulcerative colitis treated with nicotine gum and placebo and its effect on consistency of bowel movements[17]



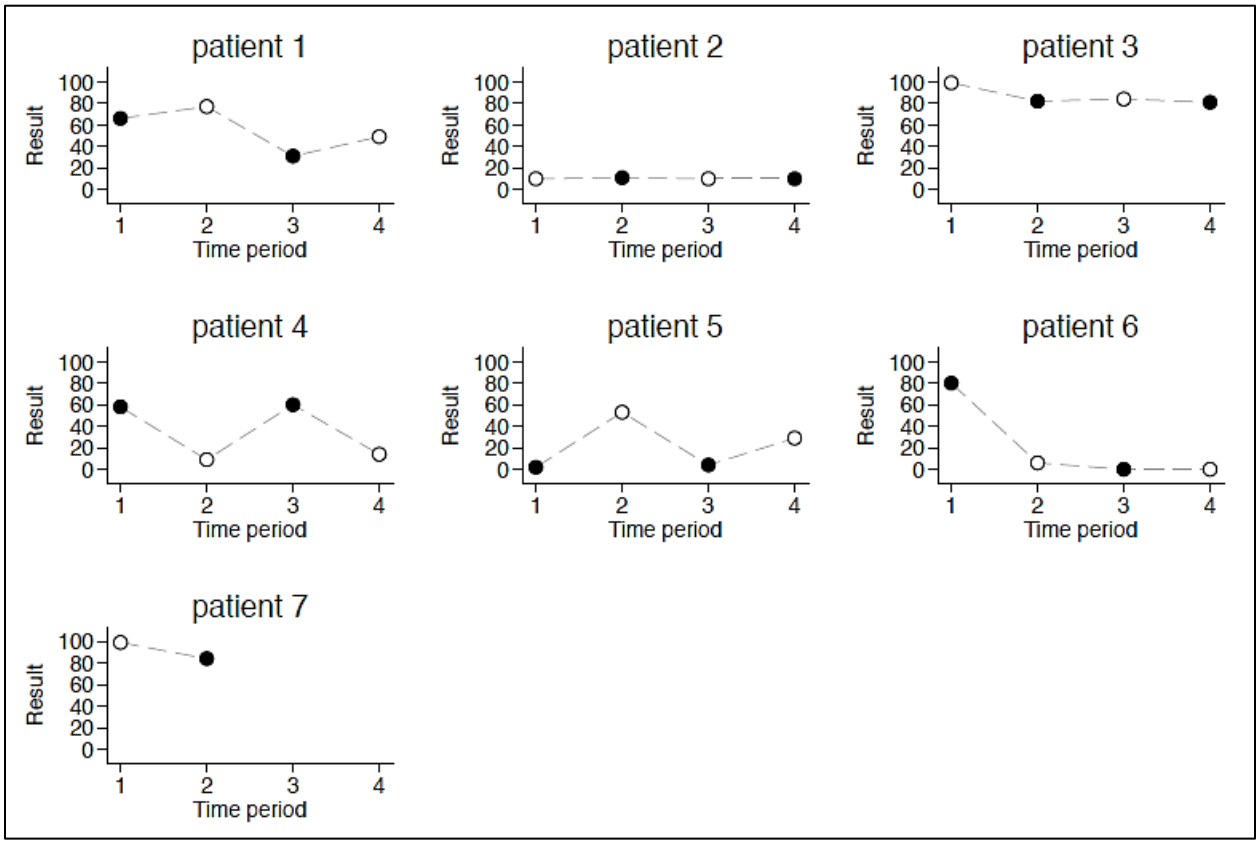
Appendix Figure 22 Legend: Data from this figure was extracted from the study published by Lashner et al in 1990, which investigates the effect of nicotine gum and placebo on consistency of bowel movements in nonsmokers with ulcerative colitis. The average treatment effect is 7.00 (-6.29 to 20.29). White circles indicate placebo gum; black circles indicate nicotine gum.

Appendix Figure 23: Nonsmokers with ulcerative colitis treated with nicotine gum and placebo and its effect on general sense of well-being[17]



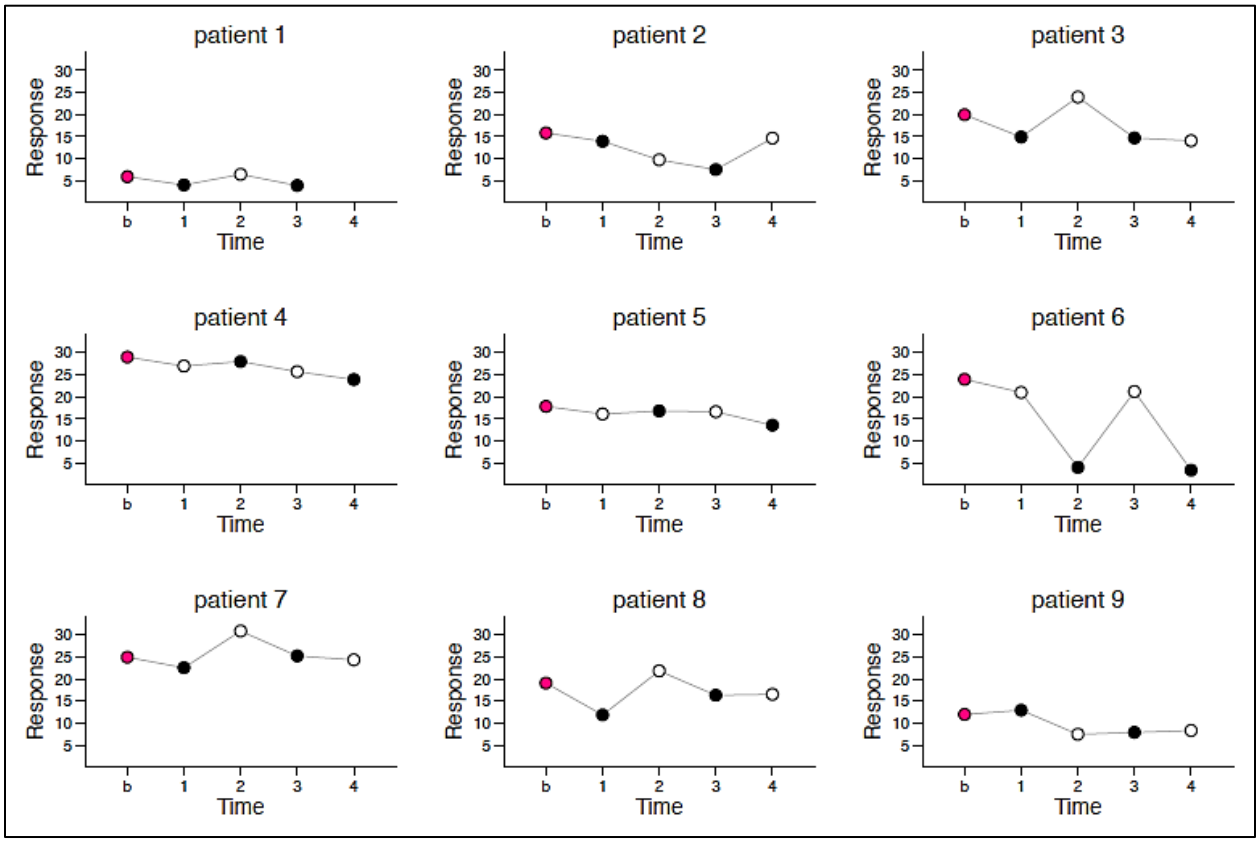
Appendix Figure 23 Legend: Data from this figure was extracted from the study published by Lashner et al in 1990, which investigates the effect of nicotine gum and placebo on general sense of well-being in nonsmokers with ulcerative colitis. The average treatment effect is -6.54 (-23.62 to 10.56). White circles indicate placebo gum; black circles indicate nicotine gum.

Appendix Figure 24: Nonsmokers with ulcerative colitis treated with nicotine gum and placebo and its effect on hematochezia[17]



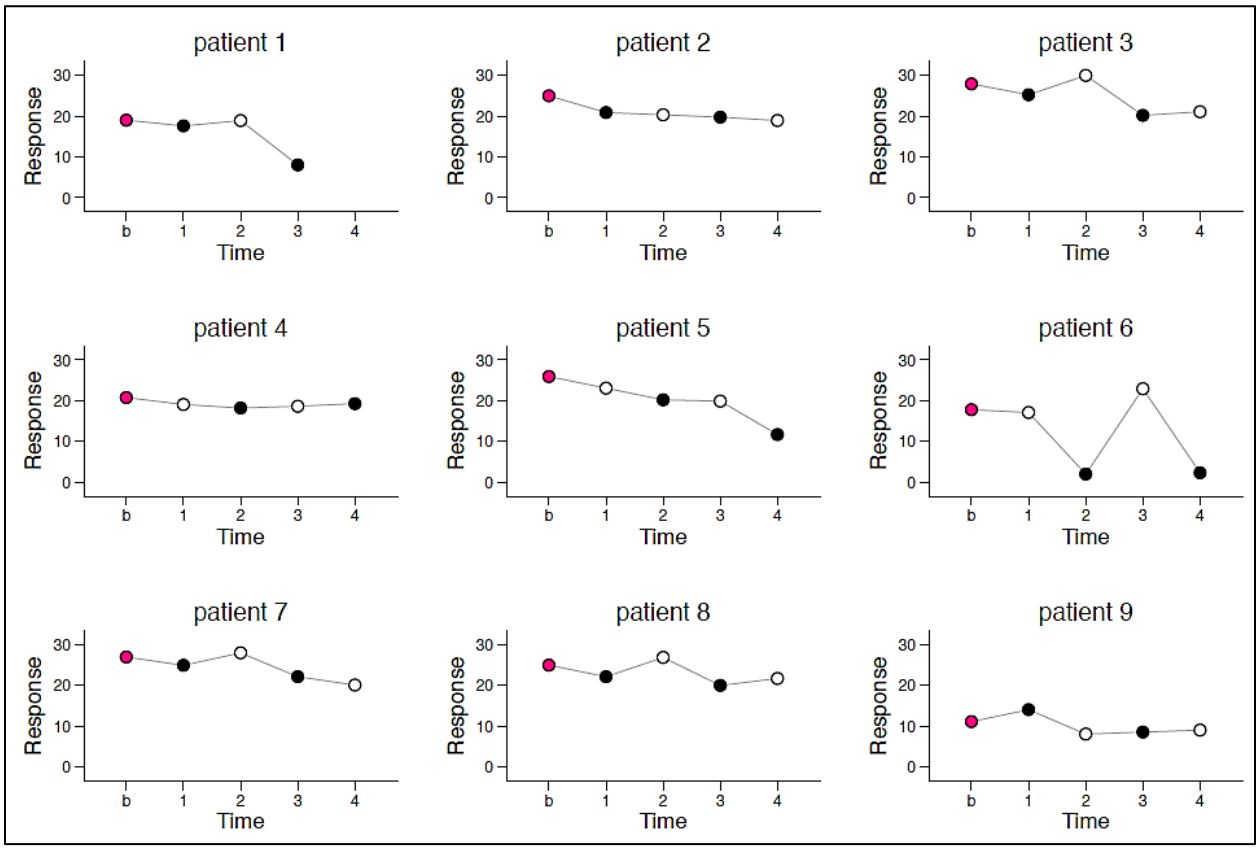
Appendix Figure 24 Legend: Data from this figure was extracted from the study published by Lashner et al in 1990, which investigates the effect of nicotine gum and placebo on hematochezia in nonsmokers with ulcerative colitis. The average treatment effect is 2.35 (-17.21 to 21.90). White circles indicate placebo gum; black circles indicate nicotine gum.

Appendix Figure 25: Patients with chronic depression and a diagnosis of major depression or dysthymia treated with sulpiride and placebo and its effect on anxiety[18]



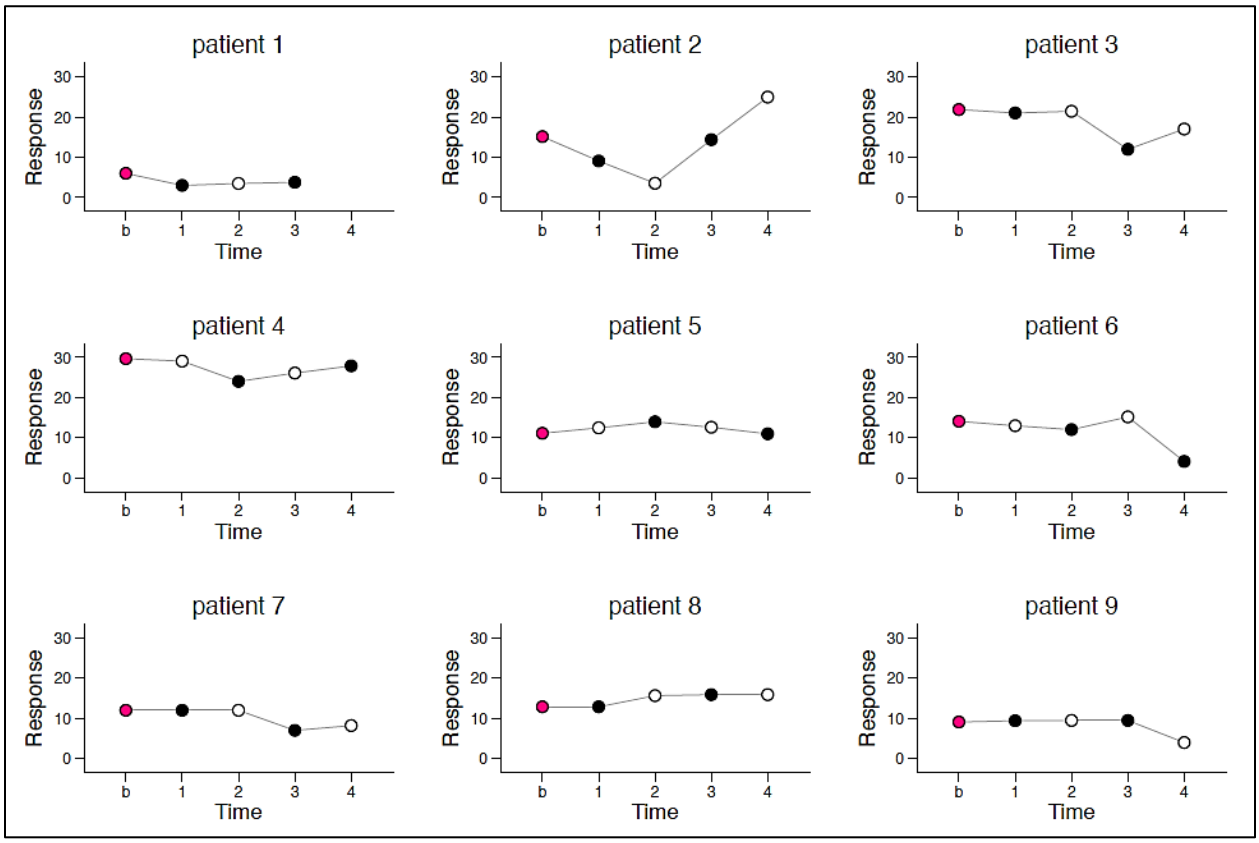
Appendix Figure 25 Legend: Data from this figure was extracted from the study published by Maier et al in 1994, which investigates the effect of sulpiride and placebo on anxiety in patients with chronic depression and a diagnosis of major depression or dysthymia. The average treatment effect is -3.81 (-7.22 to -0.40). Red circles indicate baseline; white circles indicate placebo; black circles indicate sulpiride.

Appendix Figure 26: Patients with chronic depression and a diagnosis of major depression or dysthymia treated with sulpiride and placebo and its effect on depressed mood[18]



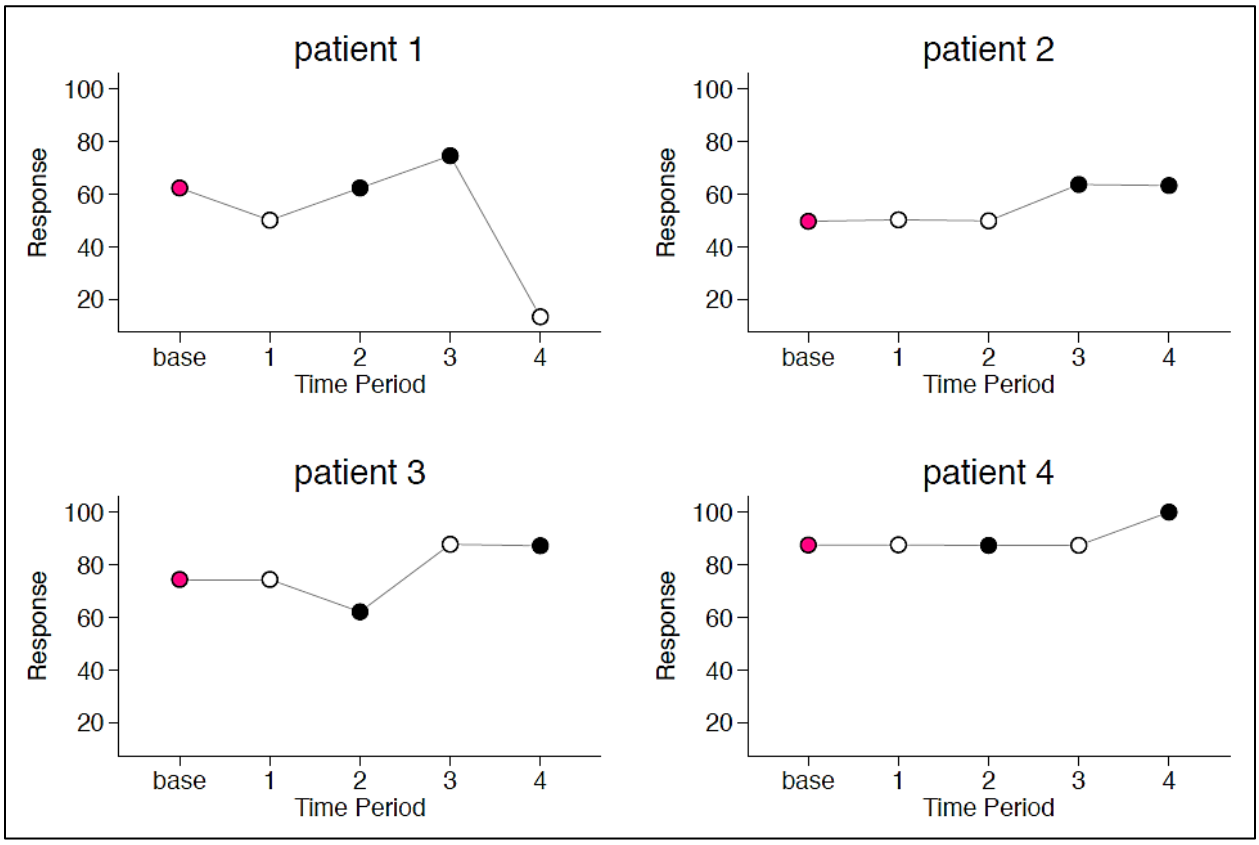
Appendix Figure 26 Legend: Data from this figure was extracted from the study published by Maier et al in 1994, which investigates the effect of sulpiride and placebo on depressed mood in patients with chronic depression and a diagnosis of major depression or dysthymia. The average treatment effect is -3.63 (-7.40 to 0.15). Red circles indicate baseline; white circles indicate placebo; black circles indicate sulpiride.

Appendix Figure 27: Patients with chronic depression and a diagnosis of major depression or dysthymia treated with sulpiride and placebo and its effect on somatization[18]



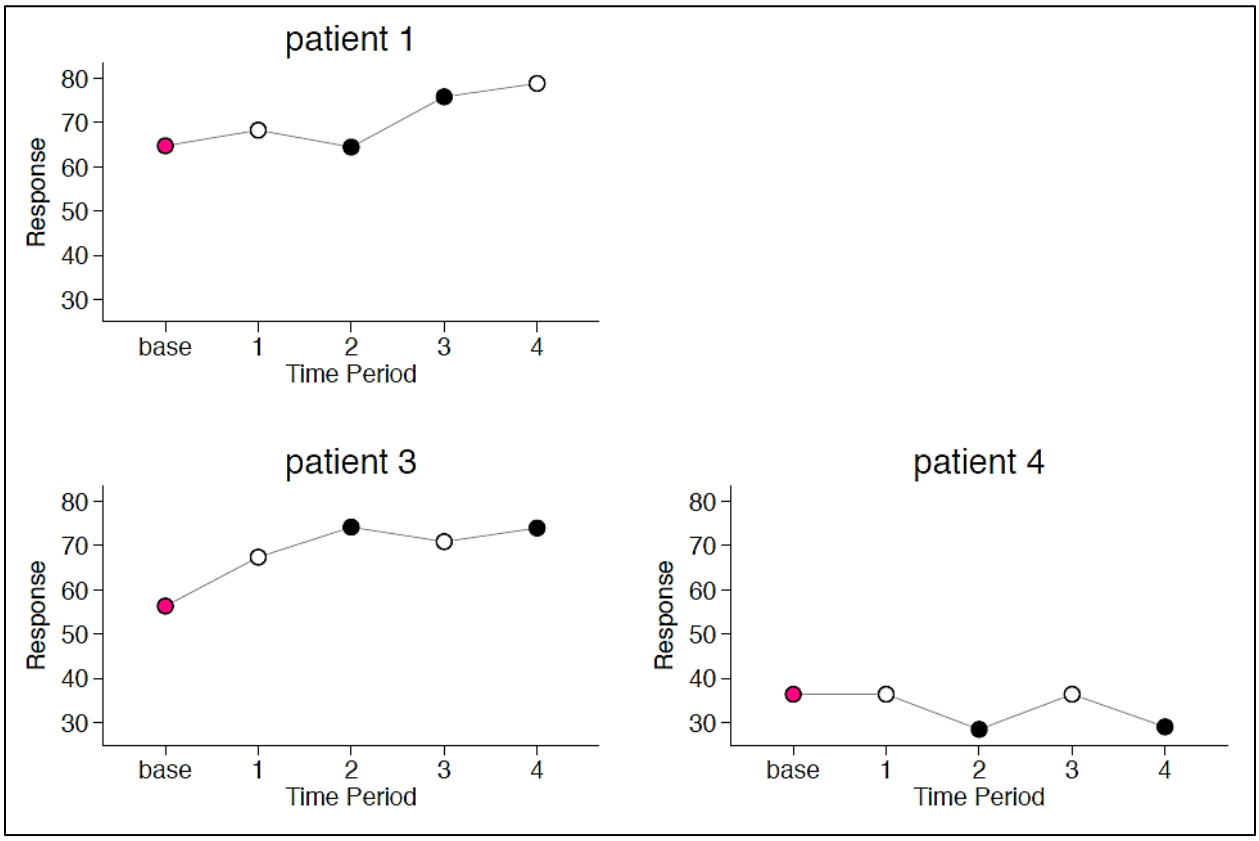
Appendix Figure 27 Legend: Data from this figure was extracted from the study published by Maier et al in 1994, which investigates the effect of sulpiride and placebo on somatization in patients with chronic depression and a diagnosis of major depression or dysthymia. The average treatment effect is -1.50 (-4.20 to 1.21). Red circles indicate baseline; white circles indicate placebo; black circles indicate sulpiride.

Appendix Figure 28: Patients with ataxia from traumatic brain injury treated with ondansetron and placebo and its effect on lower extremity ataxia[19]



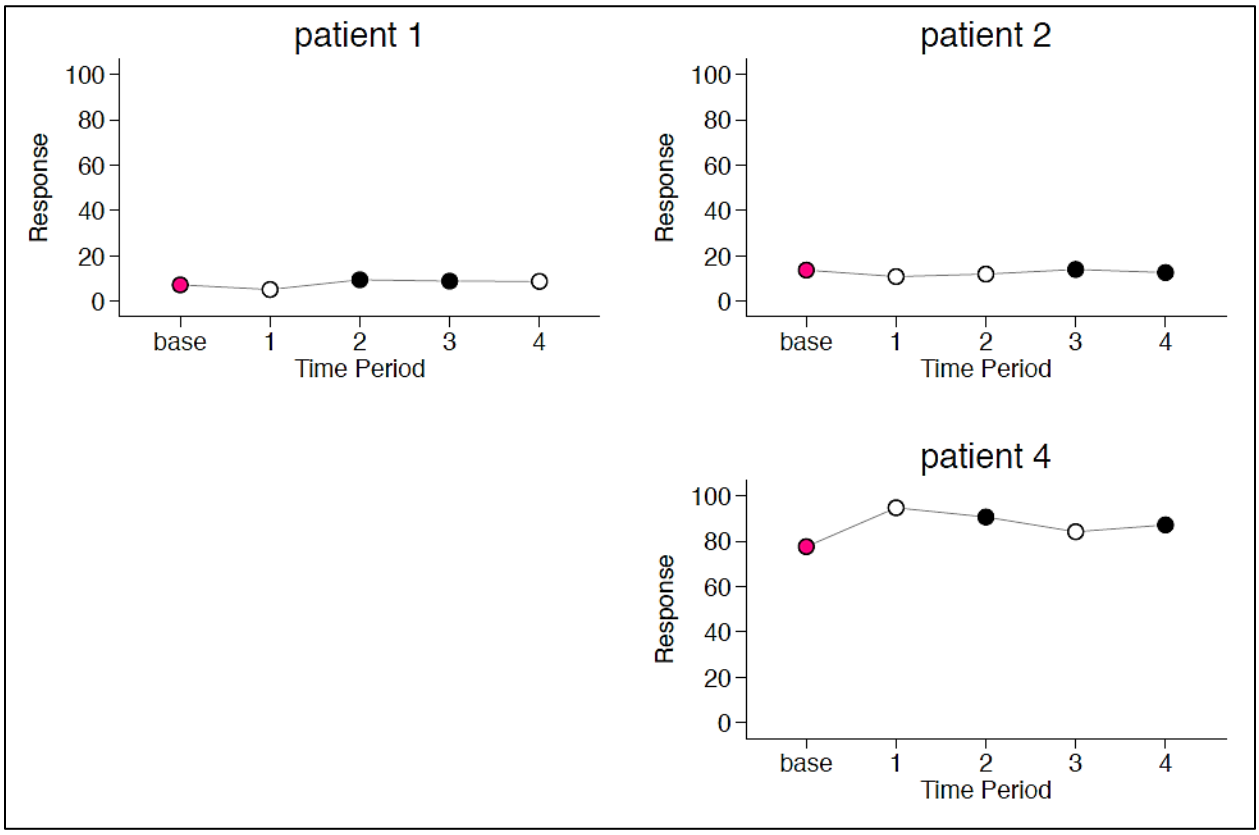
Appendix Figure 28 Legend: Data from this figure was extracted from the study published by Mandelcorn et al in 2004, which investigates the effect of ondansetron and placebo on lower extremity ataxia in patients with ataxia from traumatic brain injury. Each patient received the same treatment. The average treatment effect is 12.49 (-0.85 to 25.84). Red circles indicate baseline; white circles indicate placebo; black circles indicate ondansetron.

Appendix Figure 29: Patients with ataxia from traumatic brain injury treated with ondansetron and placebo and its effect on self-assessment score[19]



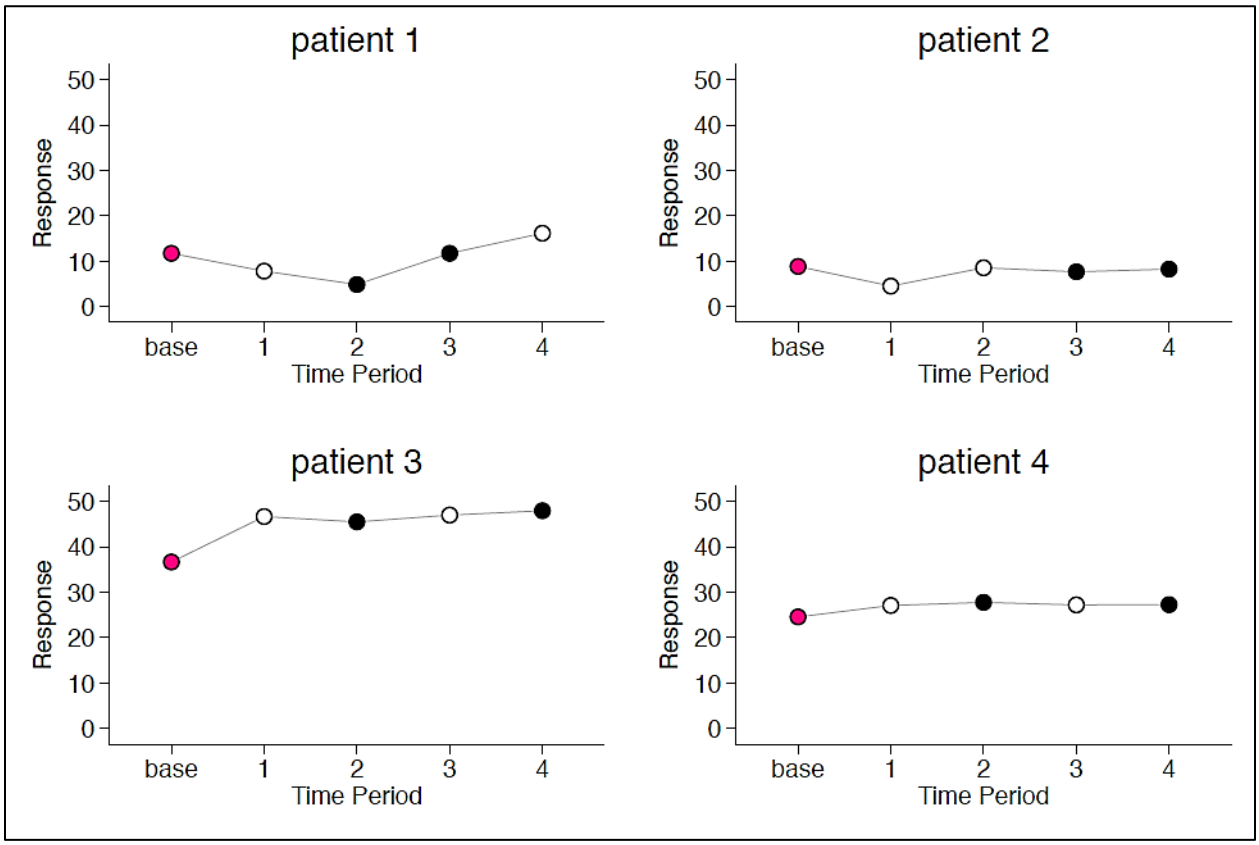
Appendix Figure 29 Legend: Data from this figure was extracted from the study published by Mandelcorn et al in 2004, which investigates the effect of ondansetron and placebo on self-assessment score in patients with ataxia from traumatic brain injury. The average treatment effect is -2.05 (-8.43 to 4.33). Red circles indicate baseline; white circles indicate placebo; black circles indicate ondansetron.

Appendix Figure 30: Patients with ataxia from traumatic brain injury treated with ondansetron and placebo and its effect on truncal ataxia[19]



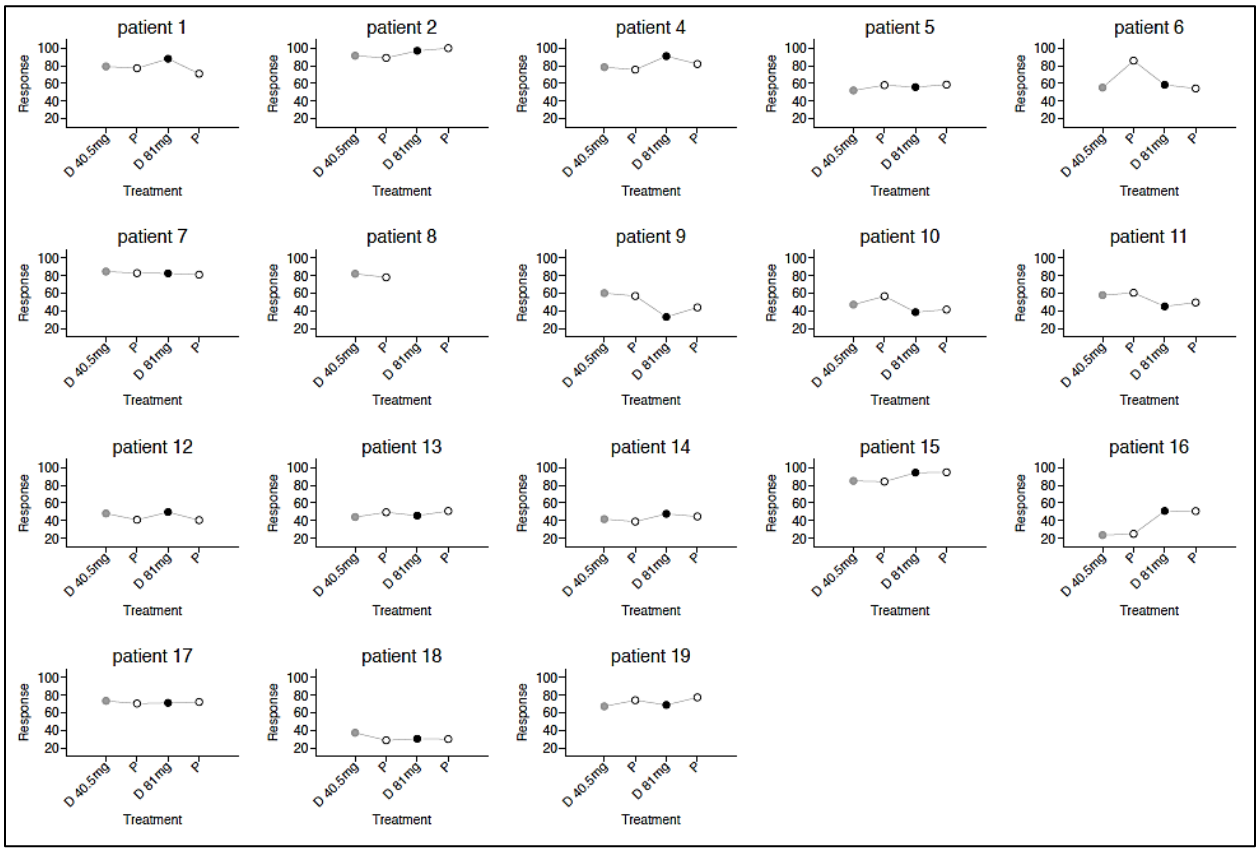
Appendix Figure 30 Legend: Data from this figure was extracted from the study published by Mandelcorn et al in 2004, which investigates the effect of ondansetron and placebo on truncal ataxia in patients with ataxia from traumatic brain injury. The average treatment effect is 1.20 (-2.06 to 4.45). Red circles indicate baseline; white circles indicate placebo; black circles indicate ondansetron.

Appendix Figure 31: Patients with ataxia from traumatic brain injury treated with ondansetron and placebo and its effect on upper extremity ataxia[19]



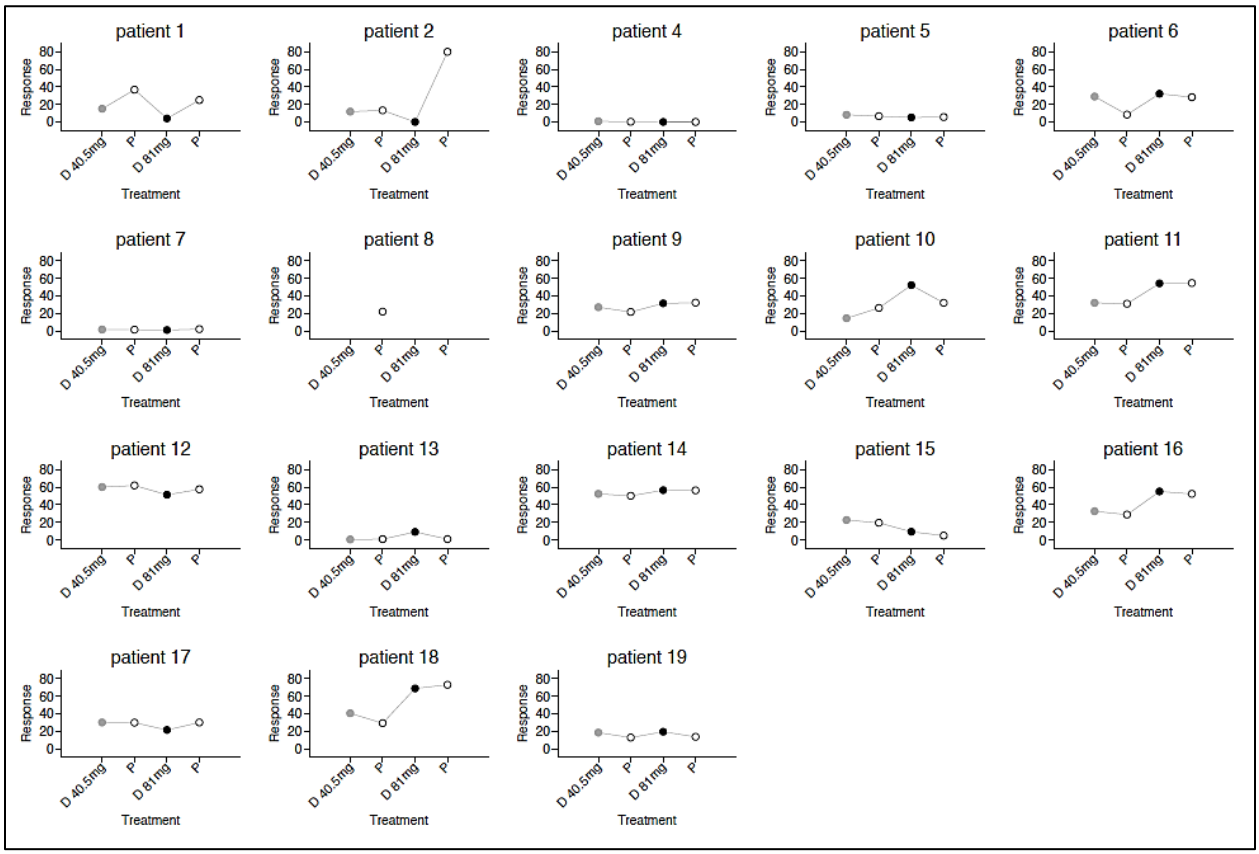
Appendix Figure 31 Legend: Data from this figure was extracted from the study published by Mandelcorn et al in 2004, which investigates the effect of ondansetron and placebo on upper extremity ataxia in patients with ataxia from traumatic brain injury. The average treatment effect is -0.50 (-3.10 to 2.10). Red circles indicate baseline; white circles indicate placebo; black circles indicate ondansetron.

Appendix Figure 32: Patients with chronic neuropathic pain treated with oral dextromethorphan and placebo and its effect on VAS pain intensity[20]



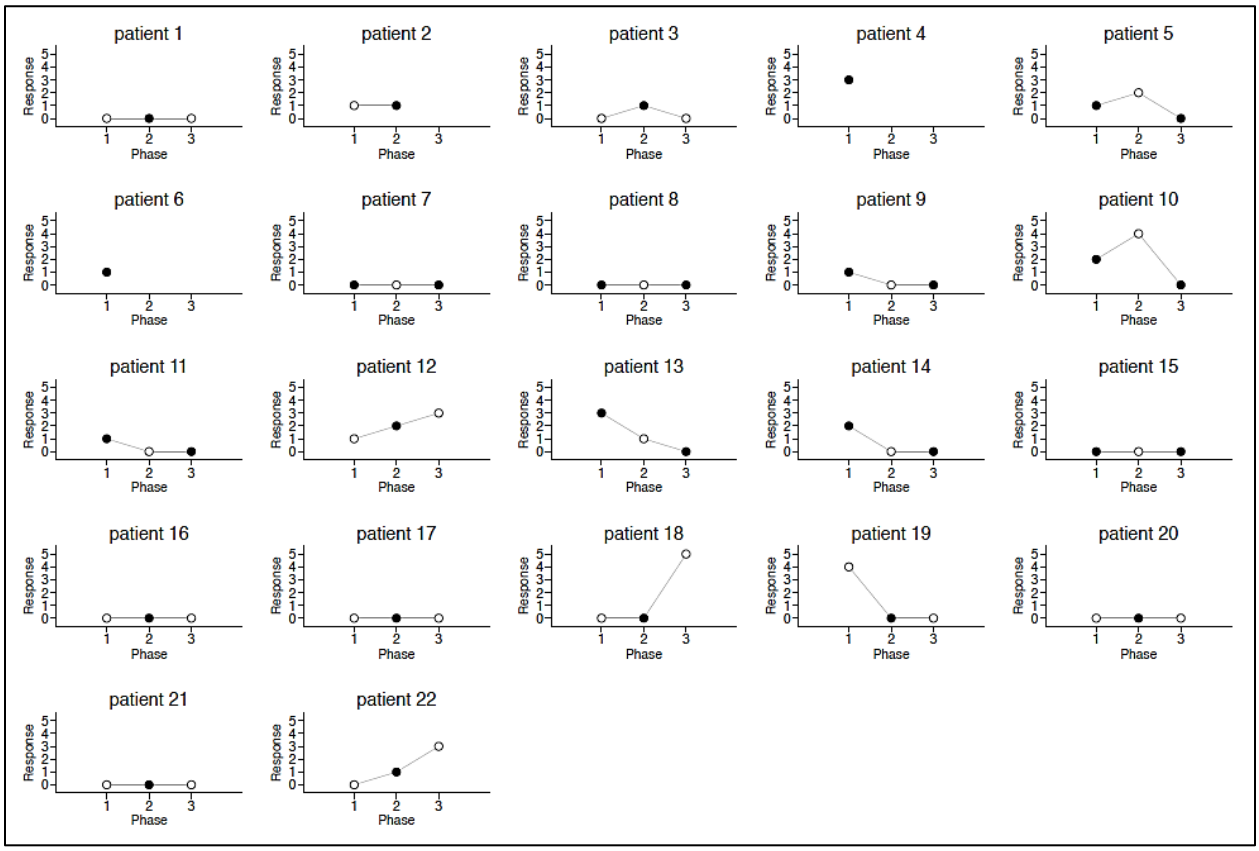
Appendix Figure 32 Legend: Data from this figure was extracted from the study published by McQuay et al in 1994, which investigates the effect of oral dextromethorphan and placebo on VAS pain intensity in patients with chronic neuropathic pain. The average treatment effect is -1.06 (-5.16 to 3.04). Grey circles indicate dextromethorphan 40.5 mg daily; black circles indicate dextromethorphan 81 mg daily; white circles indicate placebo.

Appendix Figure 33: Patients with chronic neuropathic pain treated with oral dextromethorphan and placebo and its effect on VAS relief intensity[20]



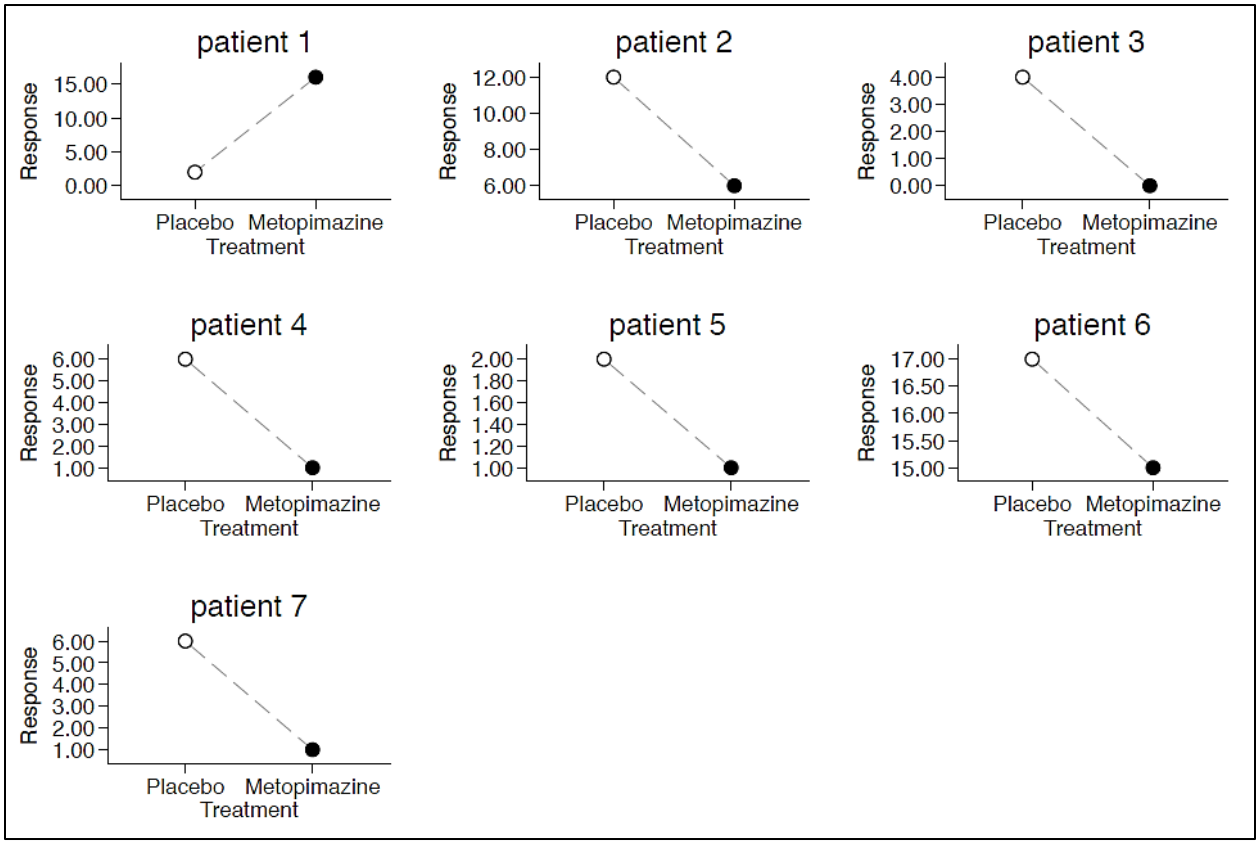
Appendix Figure 33 Legend: Data from this figure was extracted from the study published by McQuay et al in 1994, which investigates the effect of oral dextromethorphan and placebo on VAS relief intensity in patients with chronic neuropathic pain. The average treatment effect is -3.86 (-11.11 to 3.40). Grey circles indicate dextromethorphan 40.5 mg daily; black circles indicate dextromethorphan 81 mg daily; white circles indicate placebo.

Appendix Figure 34: Patients with unstable angina at rest treated with continuous and intermittent injection of isosorbide dinitrate and its effect on incidence of angina[21]



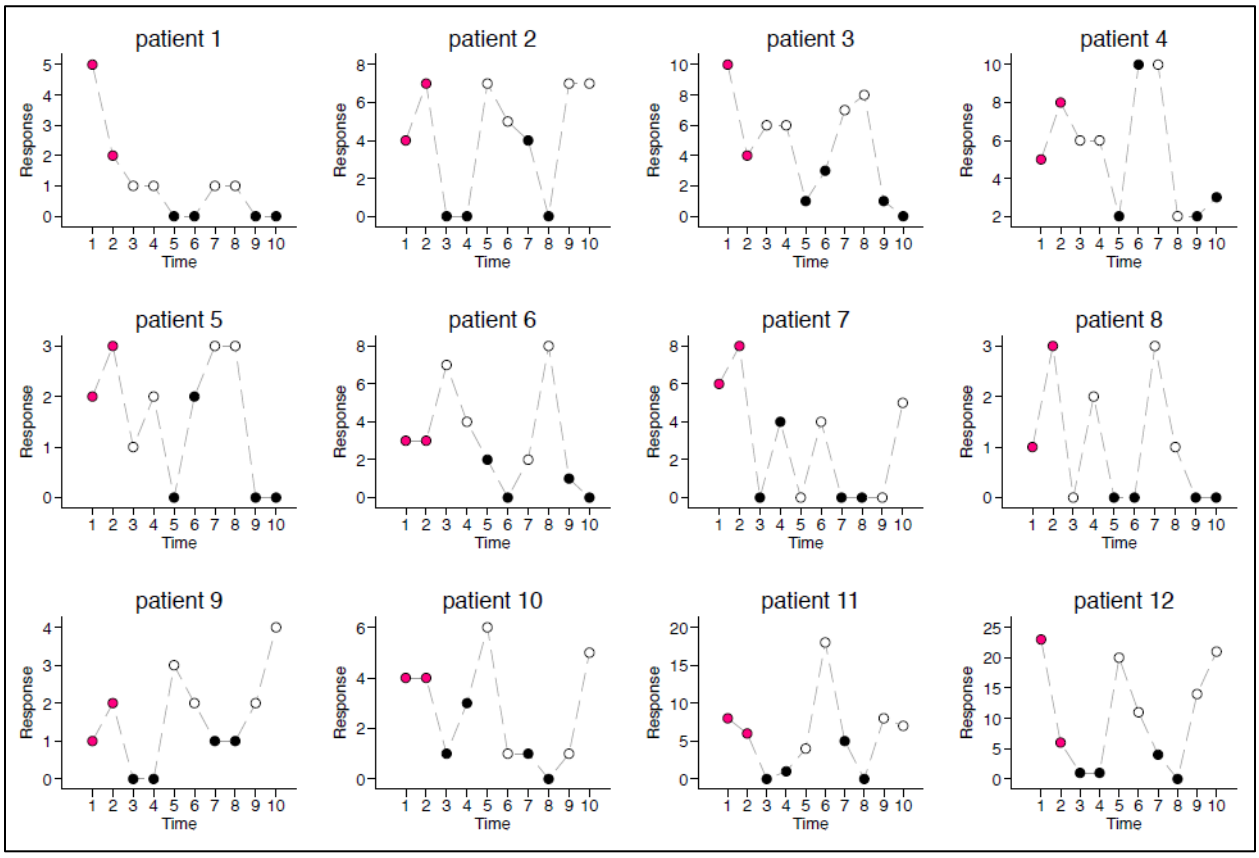
Appendix Figure 34 Legend: Data from this figure was extracted from the study published by Miyazaki et al in 1995, which investigates the effect of continuous and intermittent injection of isosorbide dinitrate on incidence of angina in patients with unstable angina. The average treatment effect is 0.47 (-0.32 to 1.26). White circles indicate continuous injection; black circles indicate intermittent injection.

Appendix Figure 35: Children with brain tumors receiving highly emetogenic therapy treated with ondansetron/metopimazine and ondansetron monotherapy and its effect on emetic episodes per day[22]



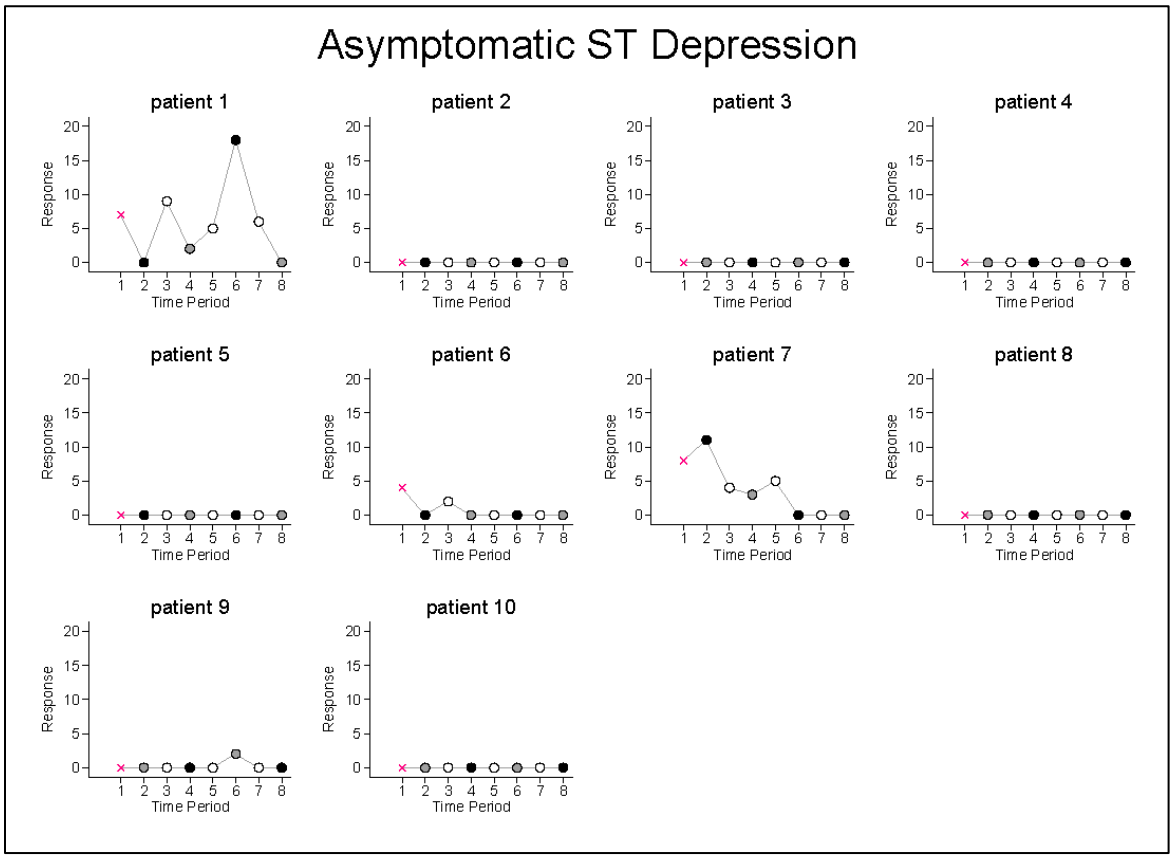
Appendix Figure 35 Legend: Data from this figure was extracted from the study published by Nathan et al in 2006, which investigates the effect of ondansetron/metopimazine and ondansetron monotherapy on emetic episodes per day in children with brain tumors receiving highly emetogenic therapy. The average treatment effect is -0.56 (-1.74 to 0.62). White circles indicate placebo; black circles indicate metopimazine.

Appendix Figure 36: Patients with unstable angina at rest treated with oral verapamil and placebo and its effect on ischemic attacks[23]



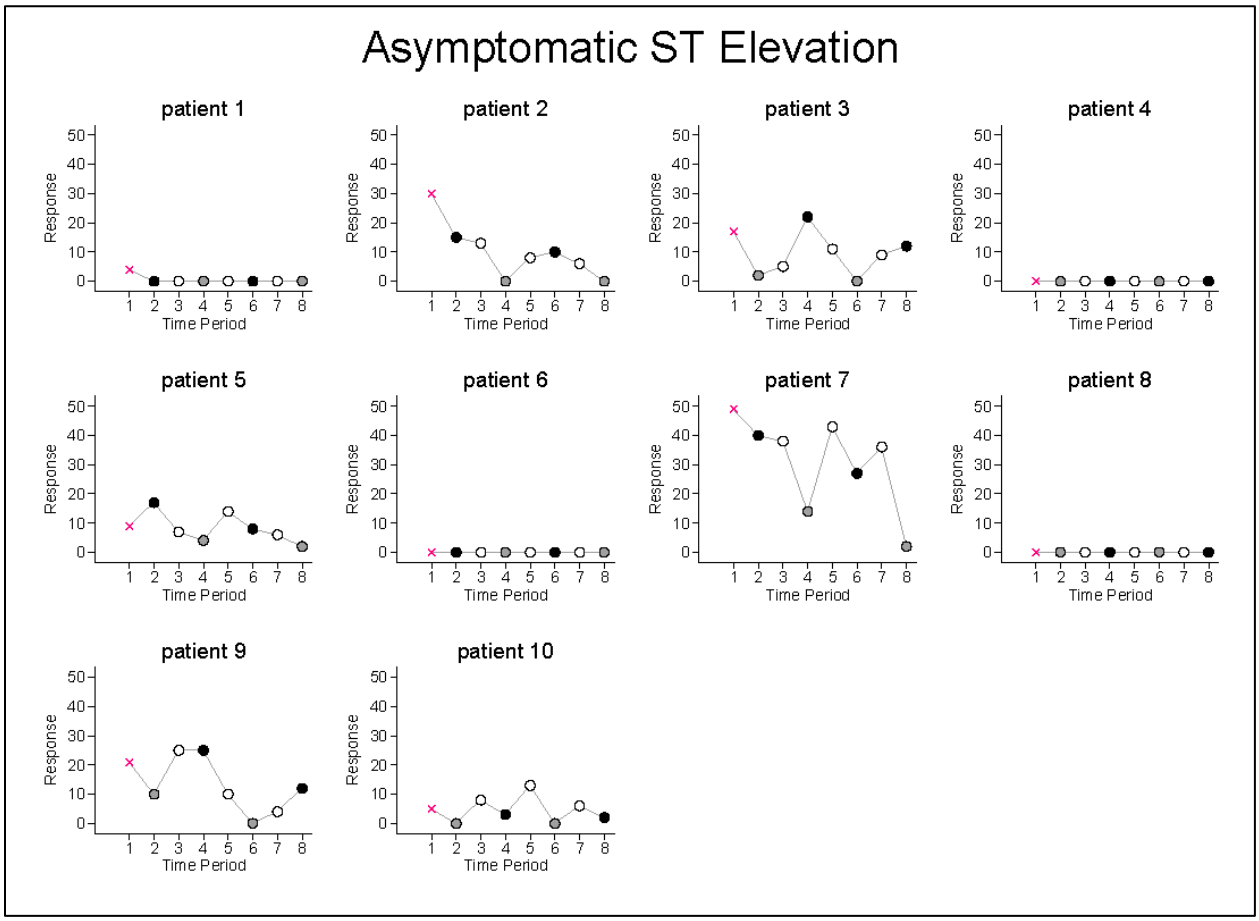
Appendix Figure 36 Legend: Data from this figure was extracted from the study published by Parodi et al in 1979, which investigates the effect of oral verapamil and placebo on ischemic attacks in patients with unstable angina. The average treatment effect is -1.63 (-2.10 to -1.17). Red circles indicate baseline; white circles indicate placebo; black circles indicate verapamil.

Appendix Figure 37: Patients with unstable angina at rest treated with verapamil, propranolol and placebo and its effect on asymptomatic ST depression[24]



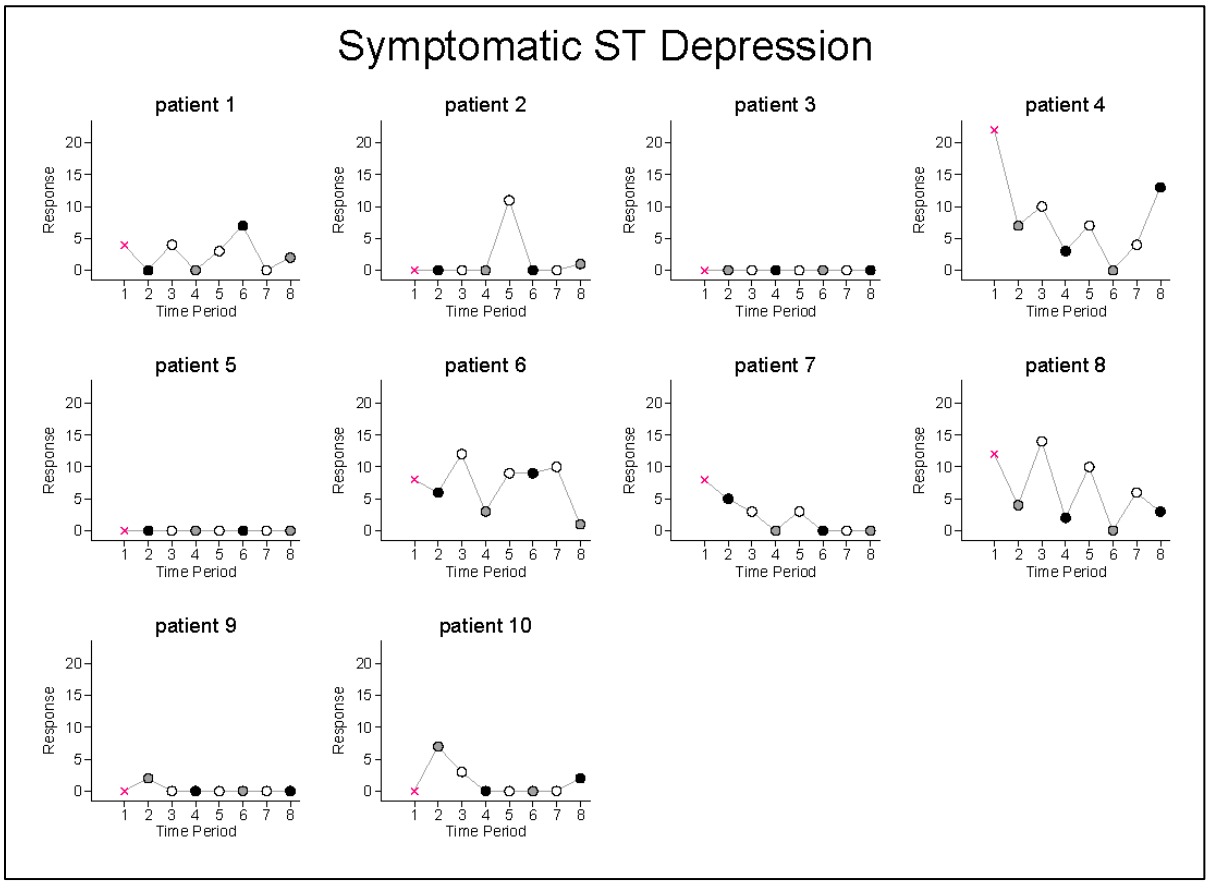
Appendix Figure 37 Legend: Data from this figure was extracted from the study published by Parodi et al in 1986, which investigates the effect of verapamil, propranolol and placebo on asymptomatic ST depression in patients with unstable angina. The average treatment effect is -0.82 (-2.54 to 0.90). Red Xs indicate baseline; white circles indicate placebo; grey circles indicate propranolol; black circles indicate verapamil.

Appendix Figure 38: Patients with unstable angina at rest treated with verapamil, propranolol and placebo and its effect on asymptomatic ST elevation[24]



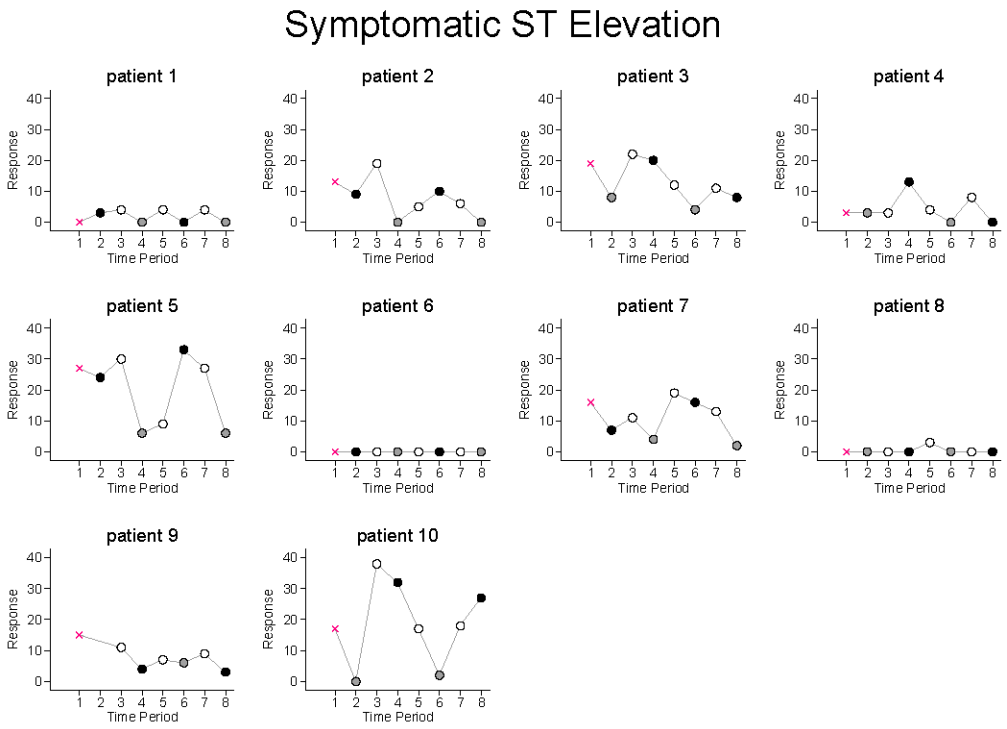
Appendix Figure 38 Legend: Data from this figure was extracted from the study published by Parodi et al in 1986, which investigates the effect of verapamil, propranolol and placebo on asymptomatic ST elevation in patients with unstable angina. The average treatment effect is -1.97 (-2.92 to -1.01). Red Xs indicate baseline; white circles indicate placebo; grey circles indicate propranolol; black circles indicate verapamil.

Appendix Figure 39: Patients with unstable angina at rest treated with verapamil, propranolol and placebo and its effect on symptomatic ST depression[24]



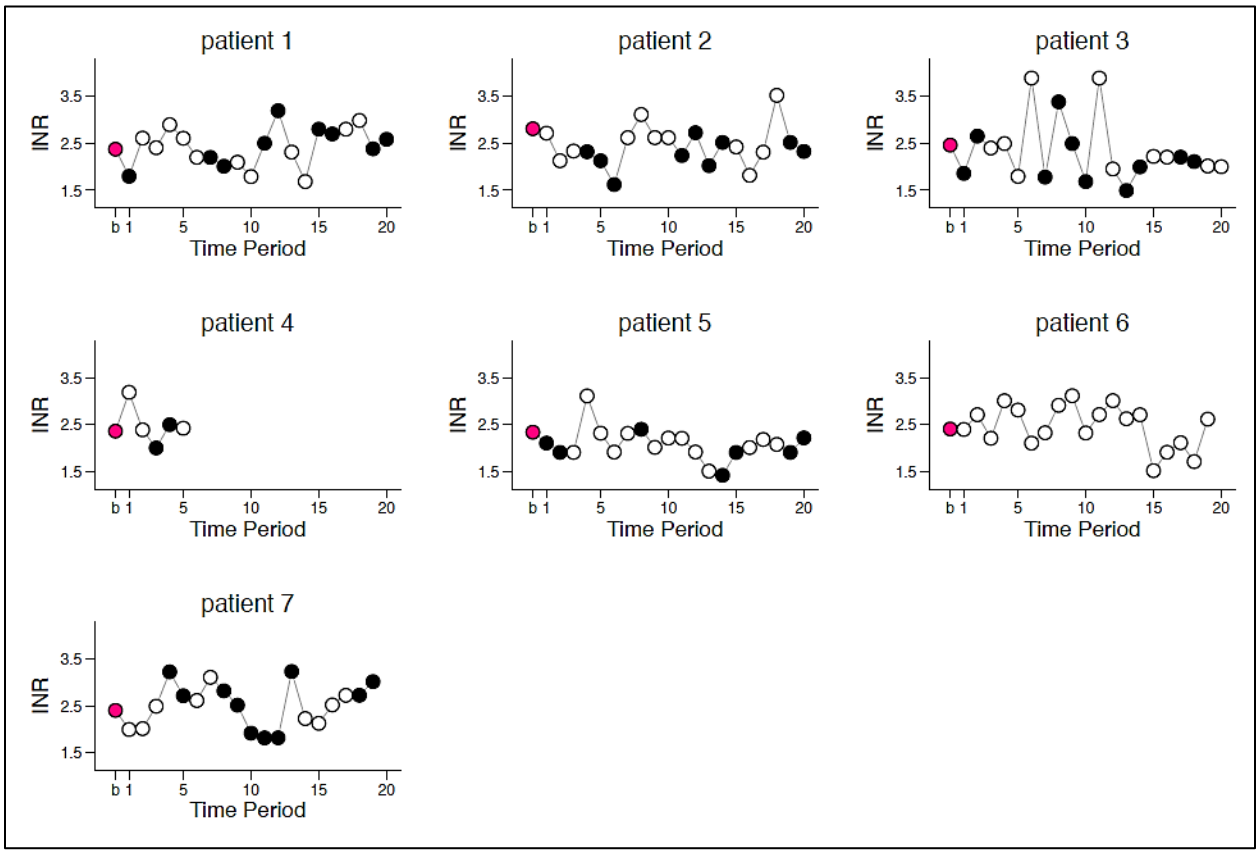
Appendix Figure 39 Legend: Data from this figure was extracted from the study published by Parodi et al in 1986, which investigates the effect of verapamil, propranolol and placebo on symptomatic ST depression in patients with unstable angina. The average treatment effect is -0.98 (-1.84 to -0.13). Red Xs indicate baseline; white circles indicate placebo; grey circles indicate propranolol; black circles indicate verapamil.

Appendix Figure 40: Patients with unstable angina at rest treated with verapamil, propranolol and placebo and its effect on symptomatic ST elevation[24]



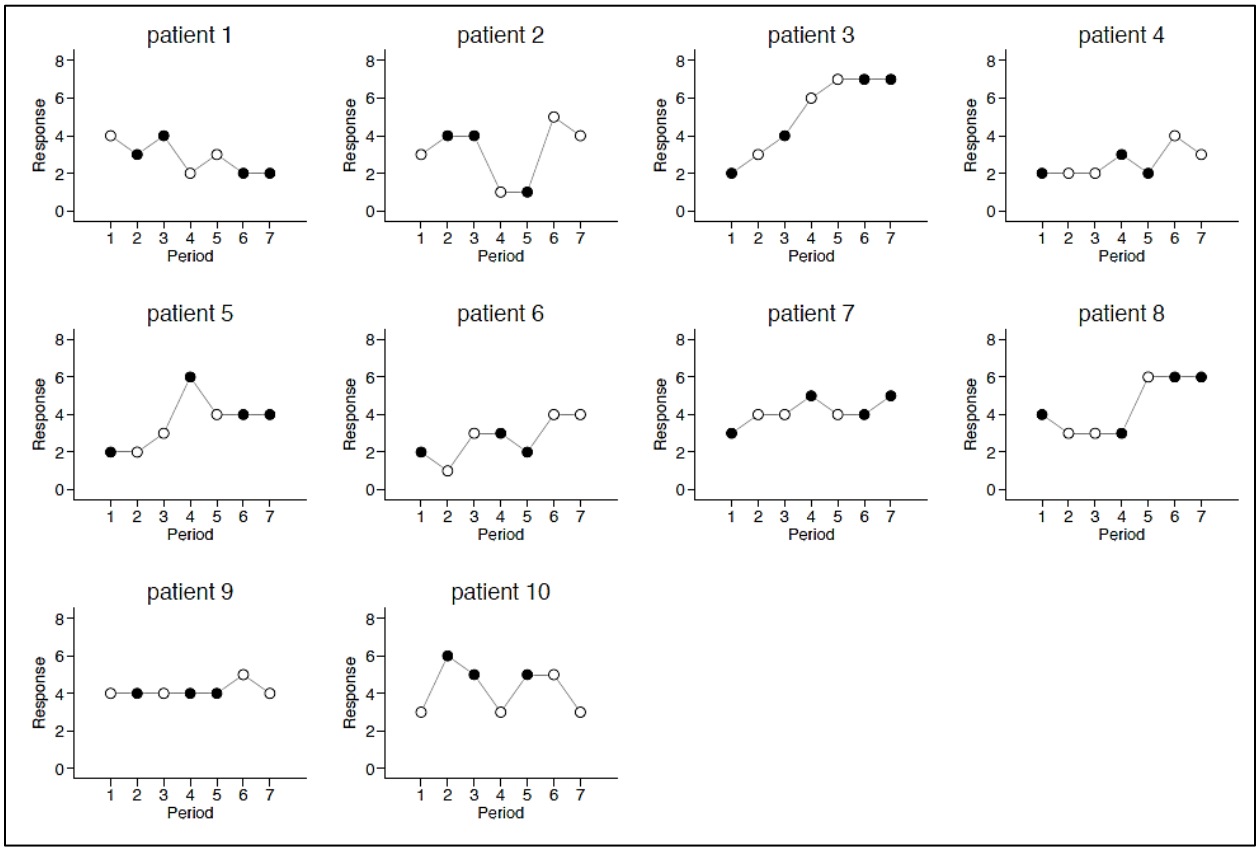
Appendix Figure 40 Legend: Data from this figure was extracted from the study published by Parodi et al in 1986, which investigates the effect of verapamil, propranolol and placebo on symptomatic ST elevation in patients with unstable angina. The average treatment effect is -1.87 (-2.72 to -1.02). Red Xs indicate baseline; white circles indicate placebo; grey circles indicate propranolol; black circles indicate verapamil.

Appendix Figure 41: Patients previously taking warfarin for either atrial fibrillation or deep vein thrombosis treated with apo-warfarin and coumadin and its effect on international normalized ratio[8]



Appendix Figure 41 Legend: Data from this figure was extracted from the study published by Pereira et al in 1995, which investigates the effect of apo-warfarin and coumadin on international normalized ratio in patients previously taking warfarin for either atrial fibrillation or deep vein thrombosis. The average treatment effect is -0.12 (-0.30 to 0.07). Red circles indicate baseline; white circles indicate Coumadin; black circles indicate apo-warfarin.

Appendix Figure 42: Parkinson's disease patients with troublesome dyskinesia treated with simvastatin and placebo and its effect on discomfort caused by troublesome dyskinesia[25]



Appendix Figure 42 Legend: Data from this figure was extracted from the study published by Tison et al in 2012, which investigates the effect of simvastatin and placebo on discomfort caused by troublesome dyskinesia in Parkinson's disease patients with troublesome dyskinesia. The average treatment effect is0.20 (-0.40 to 0.80). White circles indicate placebo; black circles indicate simvastatin.

Appendix Reference List

(1) Emmanuel AV, Kamm MA, Roy AJ, Kerstens R, Vandeplassche L. Randomised clinical trial: the efficacy of prucalopride in patients with chronic intestinal pseudo-obstruction--a double-blind, placebo-controlled, cross-over, multiple n = 1 study. *Aliment Pharmacol Ther* 2012; 35(1):48-55.

(2) Haas DC, Sheehe PR. Dextroamphetamine pilot crossover trials and n of 1 trials in patients with chronic tension-type and migraine headache. *Headache* 2004; 44(10):1029-1037.

(3) Jaeschke R, Adachi J, Guyatt G, Keller J, Wong B. Clinical usefulness of amitriptyline in fibromyalgia: the results of 23 N-of-1 randomized controlled trials. *J Rheumatol* 1991; 18(3):447-451.

(4) Johannessen T, Petersen H, Kristensen P, Fosstvedt D, Kleveland PM, Dybdahl J et al. Cimetidine on-demand in dyspepsia. Experience with randomized controlled single-subject trials. *Scand J Gastroenterol* 1992; 27(3):189-195.

(5) Mahon J, Laupacis A, Donner A, Wood T. Randomised study of n of 1 trials versus standard practice. *BMJ* 1996; 312(7038):1069-1074.

(6) March L, Irwig L, Schwarz J, Simpson J, Chock C, Brooks P. n of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthritis. *BMJ* 1994; 309(6961):1041-1045.

(7) Patel A, Jaeschke R, Guyatt GH, Keller JL, Newhouse MT. Clinical usefulness of n-of-1 randomized controlled trials in patients with nonreversible chronic airflow limitation. *Am Rev Respir Dis* 1991; 144(4):962-964.

(8) Pereira JA, Holbrook AM, Dolovich L, Goldsmith C, Thabane L, Douketis JD et al. Are brand-name and generic warfarin interchangeable? Multiple n-of-1 randomized, crossover trials. *Ann Pharmacother* 2005; 39(7-8):1188-1193.

(9) Wallace AE, Kofoed LL. Statistical analysis of single case studies in the clinical setting: the example of methylphenidate trials in children with attention-deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol* 1994; 4(3):141-150.

(10) Woodfield R, Goodyear-Smith F, Arroll B. N-of-1 trials of quinine efficacy in skeletal muscle cramps of the leg. *Br J Gen Pract* 2005; 55(512):181-185.

(11) Zucker DR, Ruthazer R, Schmid CH, Feuer JM, Fischer PA, Kieval RI et al. Lessons learned combining N-of-1 trials to assess fibromyalgia therapies. *J Rheumatol* 2006; 33(10):2069-2077.

(12) Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. *Ann Intern Med* 2014; 160(5):301-310.

(13) Lipka AF, Vrinten C, van Zwet EW, Schimmel KJ, Cornel MC, Kuijpers MR et al. Ephedrine treatment for autoimmune myasthenia gravis. *Neuromuscul Disord* 2017; 27(3):259-265.

(14) Camfield P, Gordon K, Dooley J, Camfield C. Melatonin appears ineffective in children with intellectual deficits and fragmented sleep: six "N of 1" trials. *J Child Neurol* 1996; 11(4):341-343.

(15) Hinderer SR. The supraspinal anxiolytic effect of baclofen for spasticity reduction. *Am J Phys Med Rehabil* 1990; 69(5):254-258.

(16) Langer JC, Winthrop AL, Issenman RM. The single-subject randomized trial. A useful clinical tool for assessing therapeutic efficacy in pediatric practice. *Clin Pediatr (Phila)* 1993; 32(11):654-657.

(17) Lashner BA, Hanauer SB, Silverstein MD. Testing nicotine gum for ulcerative colitis patients. Experience with single-patient trials. *Dig Dis Sci* 1990; 35(7):827-832.

(18) Maier W, Benkert O. Treatment of chronic depression with sulpiride: evidence of efficacy in placebo-controlled single case studies. *Psychopharmacology (Berl)* 1994; 115(4):495-501.

(19) Mandelcorn J, Cullen NK, Bayley MT. A preliminary study of the efficacy of ondansetron in the treatment of ataxia, poor balance and incoordination from brain injury. *Brain Inj* 2004; 18(10):1025-1039.

(20) McQuay HJ, Carroll D, Jadad AR, Glynn CJ, Jack T, Moore RA et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomised controlled crossover trial with integral n-of-1 design. *Pain* 1994; 59(1):127-133.

(21) Miyazaki S, Nonogi H, Goto Y, Sumiyoshi T, Haze K, Hiramori K. Comparison of the therapeutic efficacy of continuous and intermittent injection of isosorbide dinitrate: a randomized study on unstable angina. *Intern Med* 1995; 34(9):856-862.

(22) Nathan PC, Tomlinson G, Dupuis LL, Greenberg ML, Ota S, Bartels U et al. A pilot study of ondansetron plus metopimazine vs. ondansetron monotherapy in children receiving highly emetogenic chemotherapy: a Bayesian randomized serial N-of-1 trials design. *Support Care Cancer* 2006; 14(3):268-276.

(23) Parodi O, Maseri A, Simonetti I. Management of unstable angina at rest by verapamil. A double-blind cross-over study in coronary care unit. *Br Heart J* 1979; 41(2):167-174.

(24) Parodi O, Simonetti I, Michelassi C, Carpeggiani C, Biagini A, L'Abbate A et al. Comparison of verapamil and propranolol therapy for angina pectoris at rest: a randomized, multiple-crossover, controlled trial in the coronary care unit. *Am J Cardiol* 1986; 57(11):899-906.

(25) Tison F, Negre-Pages L, Meissner WG, Dupouy S, Li Q, Thiolat ML et al. Simvastatin decreases levodopa-induced dyskinesia in monkeys, but not in a randomized, placebo-controlled, multiple cross-over ("n-of-1") exploratory trial of simvastatin against levodopa-induced dyskinesia in Parkinson's disease patients. *Parkinsonism Relat Disord* 2013; 19(4):416-421.

(26) Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (single-patient) trials for statin-related myalgia. *Ann Intern Med* 2014; 160(5):301-310.

Appendix Table 5. Studies reporting person-level treatment effect with both fixed-effect and random-effect using a method of moments estimator

Study	Outcome	Fixed effect model	P for HTE (fixed-effects model)	Random Treatment Effect	summary_tau2	P for HTE (random-effects model)
March 1994[6]	Mean pain score on VAS taken from 2nd week of tx	-4.155 (-4.807 to -3.502)	<0.001	-7.093 (-11.939 to -2.248)	73.530	<0.001
March 1994[6]	Mean stiffness score on VAS taken from 2nd week of	-2.192 (-2.549 to -1.835)	<0.001	-5.992 (-11.280 to -0.704)	88.872	<0.001
Emmanuel 2012[1]	Bloating	-0.131 (-0.171 to -0.090)	<0.001	-0.344 (-0.619 to -0.069)	0.071	<0.001
Emmanuel 2012[1]	Pain	-0.160 (-0.209 to -0.111)	<0.001	-0.440 (-0.771 to -0.110)	0.106	<0.001
Haas 2004[2]	Chronic tension-type headache grade	0.733 (0.609 to 0.857)	<0.001	0.772 (0.454 to 1.090)	0.350	<0.001
Haas 2004[2]	Chronic tension-type headache grade	0.543 (0.394 to 0.693)	0.067	0.542 (0.354 to 0.731)	0.055	0.067
Jaeschke 1991[3]	7-point symptom scale	0.356 (0.286 to 0.426)	<0.001	0.427 (0.210 to 0.645)	0.186	<0.001
Jaeschke 1991[3]	Tender point changes count	1.072 (0.701 to 1.443)	<0.001	1.320 (0.404 to 2.236)	2.166	<0.001
Johannessen 1992[4]	6-point symptom scale	0.657 (0.530 to 0.785)	<0.001	0.698 (0.466 to 0.931)	0.382	<0.001
Joy 2014[26]	VAS myalgia score	0.119 (-2.283 to 2.521)	0.995	0.119 (-2.283 to 2.521)	0.000	0.996
Joy 2014[26]	Symptom-specific VAS	1.937 (0.179 to 3.696)	0.797	1.937 (0.179 to 3.696)	0.000	0.797
Joy 2014[26]	Pain severity score	0.086 (-0.215 to 0.387)	0.986	0.086 (-0.215 to 0.387)	0.000	0.986

Joy 2014[26]	Pain interference score	-0.016 (-0.095 to 0.064)	0.917	-0.016 (-0.095 to 0.064)	0.000	0.917
Lipka 2017[13]	Quantitative myasthenia gravis score	1.006 (0.215 to 1.797)	0.803	1.006 (0.215 to 1.797)	0.000	0.803
Lipka 2017[13]	Myasthenia gravis composite	2.952 (0.969 to 4.934)	0.177	2.891 (0.348 to 5.433)	2.631	0.177
Lipka 2017[13]	MG-ADL	1.110 (0.269 to 1.951)	0.047	1.099 (-0.277 to 2.474)	1.222	0.047
Lipka 2017[13]	VAS score	1.204 (0.124 to 2.283)	0.190	1.275 (-0.115 to 2.665)	0.739	0.190
Mahon 1996[5]	Likert Scale (1-7)	0.069 (-0.042 to 0.179)	<0.001	0.145 (-0.153 to 0.443)	0.134	<0.001
Patel 1991[7]	4-item symptom questionnaire	0.000 (-0.000 to 0.000)*	<0.001	0.000 (-0.000 to 0.000)*	0.000	<0.001
Pereira 1995[8]	INR (diff)	0.027 (-0.155 to 0.209)	0.477	0.027 (-0.155 to 0.209)	0.000	0.477
Wallace 1994[9]	Conners 15-item rating scale scores	0.759 (0.341 to 1.178)	0.747	0.759 (0.341 to 1.178)	0.000	0.747
Woodfield 2005[10]	Number of cramps	-5.395 (-7.091 to -3.699)	<0.001	-18.823 (-28.527 to -9.120)	161.582	<0.001
Woodfield 2005[10]	Total days with cramps	-7.600 (-8.420 to -6.781)	<0.001	-6.181 (-9.798 to -2.563)	26.245	<0.001
Zucker 2006[11]	FIQ	-5.019 (-8.784 to -1.254)	0.999	-5.019 (-8.784 to -1.254)	0.000	0.999

* Includes one additional trial of Prednisone therapy

Appendix Table 6. Studies reporting person-level outcomes with both fixed-effect and random-effect hierarchical linear model

Author Year	Outcome	Range of the Scales (severity)	Fixed Treatment Effect	Random Treatment Effect	P-value Person Treatment Interaction
Camfield 1996[14]	Nights without awakening	NR	0.865 (0.215 to 1.516)	0.84 (0.20 to 1.48)	0.456
Hinderer 1990[15]	Anxiety	Beck Inventory-A anxiety scale 0-3 (0 = never, 3 = almost all the time)	0.000 (0.000 to 0.000)	-1.06 (-1.88 to -0.23)	<0.001
Joy 2014[26]	Myalgia score	Visual Analogue Score for myalgia (0=none to 100=worst)	3.3812 (-2.668 to 9.430)	3.3522 (-2.617 to 9.322)	0.566
Langer 1993[16]	Vomiting	NR	-1.204 (-2.494 to 0.086)	-1.20 (-2.49 to 0.09)	0.136
Lashner 1990[17]	Symptom score: abdominal pain	Symptom scores 0-100 (0=best, 100=worst)	-3.615 (-16.982 to 9.751)	-3.62 (-15.84 to 8.61)	0.007
	Symptom score: bowel movements/day		-0.538 (-1.215 to 0.138)	-0.56 (-1.22 to 0.09)	0.001
	Symptom score: consistency of bowel movements		7.000 (-7.551 to 21.551)	7.00 (-6.29 to 20.29)	0.013
	Symptom score: hematochezia		2.308 (-17.210 to 21.826)	2.35 (-17.21 to 21.90)	0.003
	Symptom score: general sense of well-being		-6.538 (-25.352 to 12.275)	-6.54 (-23.62 to 10.56)	0.008
Maier 1994[18]	SCL-90 subscales: Depressed mood	NR	-3.536 (-6.718 to -0.354)	-3.63 (-7.40 to 0.15)	<0.001
	SCL-90 subscales: Anxiety		-3.753 (-6.582 to -0.924)	-3.81 (-7.22 to -0.40)	<0.001
	SCL-90 subscales: Somatization		-1.419 (-4.316 to 1.478)	-1.50 (-4.20 to 1.21)	0.869
Mandelcorn 2004[19]	Self-Assessment score	0–5 (0=worst, 5=best)	-2.052 (-8.865 to 4.761)	-2.05 (-8.43 to 4.33)	0.05
	Lower extremity ataxia	Fugl-Meyer: 3-point (0 cannot be performed to 2 can	12.494 (-3.155 to 28.142)	12.49 (-0.85 to 25.84)	0.025

Author Year	Outcome	Range of the Scales (severity)	Fixed Treatment Effect	Random Treatment Effect	P-value Person Treatment Interaction
		be fully performed)			
	Truncal ataxia	AMTI forceplate®: NR *Berg Balance Scale® 0–56, with a higher score indicating a better performance*	1.196 (-2.866 to 5.257)	1.20 (-2.06 to 4.45)	0.690
	Upper extremity ataxia	Purdue Pegboard Test®: pegs inserted into the board with each hand in 30 sec *Minnesota Placing Test®: reach out, grasp, and place blocks in a specific order*	-0.498 (-3.546 to 2.550)	-0.50 (-3.10 to 2.10)	0.382
McQuay 1994[20]	VAS Pain Intensity	0-100 (0 = no pain, 100 = worst possible pain)	-1.094 (-5.572 to 3.383)	-1.06 (-5.16 to 3.04)	0.004
	VAS Relief Intensity	0-100 (0 = no relief, 100 =complete pain relief)	-3.913 (-11.729 to 3.903)	-3.86 (-11.11 to 3.40)	0.038
Miyazaki 1995[21]	Incidence of angina	Either ST-segment elevation or depression at rest	0.496 (-0.206 to 1.199)	0.47 (-0.32 to 1.26)	0.125
Nathan 2006[22]	Emetic episodes per day	complete response (0 episodes/day), major response (1–2 episodes/day), or failure (>2 episodes/day)	-0.095 (-0.514 to 0.325)	-0.56 (-1.74 to 0.62)	0.001
Parodi 1979[23]	Ischemic attacks	ST elevation or depression (details NR)	-1.544 (-1.838 to -1.251)	-1.63 (-2.10 to -1.17)	0.007
Parodi 1986[24]	Asymptomatic ST elevation (After verapamil)	NR	-1.637 (-1.994 to -1.279)	-1.97 (-2.92 to -1.01)	0.110
	Asymptomatic ST depression (After verapamil)		-1.083 (-1.903 to -0.262)	-0.82 (-2.54 to 0.90)	0.401

Author Year	Outcome	Range of the Scales (severity)	Fixed Treatment Effect	Random Treatment Effect	P-value Person Treatment Interaction
	Symptomatic ST elevation (After verapamil)		-1.580 (-1.906 to -1.254)	-1.87 (-2.72 to -1.02)	<0.001
	Symptomatic ST Depression (After verapamil)		-0.990 (-1.411 to -0.569)	-0.98 (-1.84 to -0.13)	0.002
	Asymptomatic ST elevation (After propranolol)		0.100 (-0.086 to 0.286)	-1.966 (-2.917 to -1.014)	0.006
	Asymptomatic ST depression (After propranolol)		0.339 (-0.168 to 0.845)	-0.821 (-2.539 to 0.897)	0.964
	Symptomatic ST elevation (After propranolol)		-0.002 (-0.177 to 0.173)	-1.868 (-2.718 to -1.017)	0.063
	Symptomatic ST Depression (After propranolol)		-0.374 (-0.709 to -0.039)	-0.981 (-1.835 to -0.126)	0.023
Pereira 1995[8]	INR	Target INR range of 2.0–3.0		-0.12 (-0.30 to 0.07)	0.433
Tison 2012[25]	Troublesome dyskinesia	7 points scale (1=extremely uncomfortable, 7=not at all uncomfortable)		0.20 (-0.40 to 0.80)	0.593

Statistical codes for analysis results of studies reporting person-level treatment effects

Estimation of standard errors in the following studies

- Emmanuel 2012: gen SE_Intervention (or control) =SD of intervention (or control) score/square root of Intervention days (or control days)
- Haas 2004: SE was available in Table 4 of the original paper
- Jaeschke 1991, Patel 1991, March 1994, Woodfield 2005, Wallace 1994 - SE was derived using the p-value of one-sided paired t-test of the difference in score using the following code:
  generate t_stat = invt(2,p_value)
  generate se = abs(mean_outcome/t_stat)
- Johannessen 1992, Pereira 1995, Zucker 2006, Joy 2014, Lipka 2017 – SE was derived from the 95% confidence interval using the following code: generate se = (UCI - LCI) /(2*invnorm(0.975))
- Mahon 1996: SE was derived from 95% confidence interval based on Student's t distribution using the following code: generate se = (UCI - LCI) /(2*invt(DF, 0.975))

```
metan difference se_difference  if Outcome == "outcome", random          **/fixedi is used for fixed effect model

        local p = r(p_het)

        local sum_es =  r(ES)

        local sum_es_se = r(seES)

        local tau2=  r(tau2)

        local I_sq =  r(i_sq)

post `memory' ("`study'") ("`outcome'")  (`sum_es') (`sum_es_se')  (`tau2') (`I_sq') (`p')
```

Statistical codes for analysis results of studies reporting person-level outcome effects

```
egen id = group(Patient)
generate tx = 0 if Exposure == "Placebo"
        replace tx = 1 if Exposure == "Intervention"
egen period_seq = seq(), from(1) to(18) */varies based on the number of periods*/
local outcome = "Specific_outcome"
        /* fixed baselines and random treatment effects */
        xtmixed Result  tx i.id || id: tx  if Outcome == "`outcome'"  , nocons
                estimates store D
                matrix estimates = e(b)
                local point_estimate_ran_bas_ran_tx = estimates[1,1]
                local sd_estimate_rand_base_random_tx = (exp(estimates[1,10]))

                matrix variances = e(V)
                local point_se_rand_base_random_tx = sqrt(variances[1,1])
                local point_low_ran_bas_ran_tx = `point_estimate_ran_bas_ran_tx' - invnormal(0.975) * `point_se_rand_base_random_tx'
                local point_up_ran_bas_ran_tx = `point_estimate_ran_bas_ran_tx' + invnormal(0.975) * `point_se_rand_base_random_tx'

                local sd_se_rand_base_random_tx = sqrt(variances[10,10])
```

```
		local sd_lower_rand_base_random_tx = (exp(ln((`sd_estimate_rand_base_random_tx')) - invnormal(0.975) *
`sd_se_rand_base_random_tx'))

		local sd_upper_rand_base_random_tx = (exp(ln((`sd_estimate_rand_base_random_tx')) + invnormal(0.975) *
`sd_se_rand_base_random_tx'))


	/* fixed baselines and common treatment effect -- linear regression */

	xtmixed Result  tx i.id  || id: if Outcome == "`outcome'" , nocons

		estimates store E


	/* fixed baselines and person interactions */

	regress Result i.tx##i.id if Outcome == "`outcome'"

		estimates store F


	/* fixed baselines and common effects */

	regress Result tx i.id if Outcome == "`outcome'"

		estimates store G


		matrix estimates = e(b)

		local point_estimate_fix_bas_com_tx = estimates[1,1]
```

```
        matrix variances = e(V)
        local point_se_fix_bas_common_tx = sqrt(variances[1,1])
        local t_stat = `point_estimate_fix_bas_com_tx' /  `point_se_fix_bas_common_tx'
        local point_low_fix_bas_com_tx = `point_estimate_fix_bas_com_tx' - invt(e(df_r), 0.975) * `point_se_fix_bas_common_tx'
        local point_up_fix_bas_com_tx = `point_estimate_fix_bas_com_tx' + invt(e(df_r), 0.975) * `point_se_fix_bas_common_tx'

    lrtest D E
        local p_random_RANDOM_FIXED_tx =  r(p)

    lrtest F G
        local p_person_by_treat =  r(p)

    post `memory'   ("Study") ("`outcome'")
```

Please note: Depending on the outcome, xtmixed or meqrlogit or meqrpoisson was used.