

## Supplementary Materials: Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis

Ayala Shirazi, Brendon Stubbs, Lucia Gomez, Susan Moore, Fiona Gaughran, Robert J. Flanagan, James H. MacCabe and John Lally

**Table S1.** Summary of included studies comparing the prevalence of constipation among clozapine-treated patients against patients treated using other antipsychotics.

Study	Location, Design, Setting, and Constipation Assessment Method	Clozapine-Treated Patients, N, Age, % Male	Other Antipsychotics-Treated Patients, N, Age, % Male	Mean Clozapine Dose (mg) $\pm$ SD *	Number (%) Clozapine-Treated Patients with Constipation	Number (%) Patients with Constipation in Other Antipsychotics Group
Azarin <i>et al.</i> , 2001 [76]	Canada and France, RCT, Mixed in- and out-patients, Self-reported	N = 136, 37.8 $\pm$ 10.4 years, 77% male	N = 134, 39.5 $\pm$ 11.3 years, 65.4% male	642 $\pm$ 212	19 (14%)	11 (8.2%)
Baptista <i>et al.</i> , 2015 [51]	Venezuela, Cross-sectional study, Out-patients, Rome III criteria	N = 45, 46.1 $\pm$ 11.9 years, 66.7% male	N = 64, 41.7 $\pm$ 13.3 years, 40.6% male	155 $\pm$ 86	15 (33.3%)	8 (12.5%)
Brunette <i>et al.</i> , 2011 [78]	USA, RCT, Out-patients, Clinician diagnosis	N = 15, 33.3 $\pm$ 10.0 years, 80% male	N = 31, 39 $\pm$ 10.2 years, 75% male	319 $\pm$ 163.5	4 (26.7%)	4 (12.9%)
Buchanan <i>et al.</i> , 1998 [79]	USA, RCT, Out-patients, Adverse events checklist	N = 38, 41 $\pm$ 6.4 years, 65.8% male	N = 37, 40.1 $\pm$ 7.9 years, 73% male	415 $\pm$ 50.7	6 (16.1%)	7 (19%)
Every-Palmer <i>et al.</i> , 2016 [75]	New Zealand, Cross-sectional study, In-patient study, Rome III criteria	N = 20, 37 $\pm$ 8.2 years, 70% male	N = 17, 42 $\pm$ 10.9 years, 88.2% male	528 $\pm$ 161	11 (57.9%)	4 (23.5%)
Kelly <i>et al.</i> , 2003 [80]	USA, RCT, In-patients, Adverse events checklist	N = 10, 37.58 $\pm$ 8.96 years, 80% male	N = 10, 37.6 $\pm$ 9.0 years, 80% male	450 $\pm$ 0	6 (10%)	6 (60%)

Table S1. Cont.

Study	Location, Design, Setting, and Constipation Assessment Method	Clozapine-Treated Patients, N, Age, % Male	Other Antipsychotics-Treated Patients, N, Age, % Male	Mean Clozapine Dose (mg) $\pm$ SD *	Number (%) Clozapine-Treated Patients with Constipation	Number (%) Patients with Constipation in Other Antipsychotics Group
Kluge <i>et al.</i> , 2007 [73]	Germany, RCT, In-patients, Self-reported	N = 15, 36.7 $\pm$ 13 years, 47% male	N = 15, 32.8 $\pm$ 8.3 years, 33% male	266.7 $\pm$ 77.9	3 (20%)	1 (7%)
Meltzer <i>et al.</i> , 2003 [10]	USA, Canada, UK, Italy, Croatia, France, South Africa, Argentina, Chile, Czech republic, Hungary, RCT, Out-patients, Self-reported	N = 479, 37.1 $\pm$ 10.3 years, 82% male	N = 477, 37 $\pm$ 10.3 years, 79% male	274.2 $\pm$ 155	120 (25.1%)	46 (9.6%)
Naber <i>et al.</i> , 2005 [81]	Germany, RCT, In-patients, Self-reported	N = 57, 35.2 $\pm$ 10.8 years, 61.4% male	N = 57, 32.9 $\pm$ 10.4 years, 61.4% male	209 $\pm$ 91	12 (21%)	0 (0%)
Tang <i>et al.</i> , 2011 [74]	China, RCT, In-patients, Adverse events checklist	N = 30, 28.6 $\pm$ 8.5 years, 61% male	N = 32, 28.4 $\pm$ 9 years, 60% male	No mean stated (range 200–500)	22 (73.3%)	4 (12.5%)
Tolleffson <i>et al.</i> , 2001 [77]	UK, Belgium, Italy, Finland, Spain, Germany, Denmark, France, Norway, Portugal, South Africa, Sweden, Switzerland, Ireland, RCT, Mixed in- and out-patients, Self-reported	N = 90, 38.6 $\pm$ 10.6 years, 0% male	N = 90, 38.6 $\pm$ 10.6 years, 0% male	303.6 $\pm$ 108.7	17 (18.9%)	6 (6.7%)

\* In clozapine-treated patients.

**Table S2.** Summary of non-controlled studies included measuring the prevalence of constipation in clozapine-treated patients.

Study	Location, Design and Setting	Clozapine-Treated Patients, N, Age, % Male	Mean Clozapine Dose (mg) $\pm$ SD	Number (%) Clozapine-Treated Patients with Constipation
Aamani <i>et al.</i> , 2015 [58]	India, Prospective cohort, In-patients, Clinician diagnosis	N = 30, Mean age not stated, 70% males	450 $\pm$ not stated	7 (24%)
Antonacci & de Groot, 2000 [50]	USA, Retrospective cohort, In-patients, Self-reported	N = 33, 40.2 $\pm$ 9.7 years, 51.1% males	400 $\pm$ not stated	10 (30.3%)
Bailey, 2015 [57]	UK, Retrospective cohort, Out-patients, Laxative use	N = 202, 44.6 $\pm$ not stated, 69.8% males	393.8 $\pm$ not stated	71 (35%)
Centorrino <i>et al.</i> , 1994 [72]	USA, Cross-sectional, Out-patients, Adverse events checklist	N = 44, 36 $\pm$ 9.1 years, 75% males	294 $\pm$ 165	14 (32%)
De Leon, 2003 [17]	USA, Prospective cohort, In-patients, Adverse events checklist	N = 27, 44.8 $\pm$ 9.6 years, 44% males	600 $\pm$ 0	9 (33%)
Drew, 1999 [69]	Australia, Retrospective cohort, Out-patients, Adverse events checklist	N = 24, 34.5 $\pm$ 8.5 years, 56% males	410 $\pm$ not stated	5 (20.8%)
Dutt <i>et al.</i> , 2010 [49]	India, Prospective cohort, In-patients, Clinician diagnosis	N = 51, 32.1 $\pm$ 6.9 years, 80.4% males	298.97 $\pm$ 94.3	8 (15.6%)

Table S2. Cont.

Study	Location, Design and Setting	Clozapine-Treated Patients, N, Age, % Male	Mean Clozapine Dose (mg) $\pm$ SD	Number (%) Clozapine-Treated Patients with Constipation
Ebrahim <i>et al.</i> , 1994 [65]	USA, Prospective cohort, In-patients, Self-reported	N = 27, 33.8 $\pm$ 6.87 years, 100% males	558 $\pm$ 210	18 (66%)
Faasen <i>et al.</i> , 2014 [71]	South Africa, Cross-sectional, Out-patients, Self-reported	N = 29, 40.1 $\pm$ 9.9 years, 90% males	319.8 $\pm$ 158.3	13 (44.8%)
Golden, 2008 [62]	South Africa, RCT, Out-patients, Clinician diagnosis	N = 36, 39.8 $\pm$ 9.4 years, 64% males	200 $\pm$ 0	3 (8.3%)
Hayes and Gibler, 1995 [59]	USA, Retrospective cohort, In-patients, Self-reported	N = 53, Mean age not stated, % males not stated	Mean dose not stated	32 (60%)
Honer <i>et al.</i> , 2006 [63]	Canada, Germany, China, UK, RCT, Mixed in- and out- patients, Adverse events checklist	N = 33, 34.9 $\pm$ 8.5 years, 74% males	492 $\pm$ 131	7 (21%)
Hynes <i>et al.</i> , 2015 [24]	UK, Outpatients, Cross-sectional, Adverse events checklist	N = 110, 42 $\pm$ 10.1 years, 87% males	332 $\pm$ 134	53 (48%)
Kelly <i>et al.</i> , 2015 [64]	USA, RCT, Mixed in- and out-patients, Adverse events checklist	N = 23, 42.3 $\pm$ 11 years, 78% males	433.7 $\pm$ 140.1	10 (43%)

Table S2. Cont.

Study	Location, Design and Setting	Clozapine-Treated Patients, N, Age, % Male	Mean Clozapine Dose (mg) $\pm$ SD	Number (%) Clozapine-Treated Patients with Constipation
Kim <i>et al.</i> , 2009 [66]	South Korea, Prospective cohort, Outpatients, Self-reported	N = 19, 36.4 $\pm$ 7.1 years, 69.2% males	600 $\pm$ not stated	4 (21%)
Kishi <i>et al.</i> , 2013 [61]	Japan, Prospective cohort, In-patients, Clinician diagnosis	N = 38, 47.6 $\pm$ 2.5 years, 47.4% males	328 $\pm$ not stated	25 (65.8%)
Lieberman <i>et al.</i> , 1994 [60]	USA, Prospective cohort, In-patients, Adverse events checklist	N = 77, 28.2 $\pm$ 6.1 years, 67% males	458 $\pm$ 222	41 (53.3%)
Lokshin, 1999 [48]	Israel, Retrospective cohort, In-patients, Self-reported	N = 59, 37.6 $\pm$ not stated, 67.8% males	202 $\pm$ not stated	7 (12%)
Spina <i>et al.</i> , 2000 [68]	Italy, Prospective cohort, Out-patients, Clinician diagnosis	N = 45, 38.1 $\pm$ 10.4 years, 78% males	309 $\pm$ 63	3 (6.7%)
Srivastava, 2002 [56]	India, Retrospective cohort, Out-patients, Adverse events checklist	N = 15, 30.6 $\pm$ 6.2 years, 60% males	248.21 $\pm$ not stated	1 (6.7%)
Yusufi <i>et al.</i> , 2007 [70]	UK, Cross-sectional, In-patients, Adverse events checklist	N = 103, 39.3 $\pm$ 8.8 years, 69% males	456 $\pm$ 209	35 (34%)