Appendix B: Summary of evidence

Table 1. Pharmacological interventions for weight management

Studies about metformin						
Reference	Study type	Intervention	Population	Result	Direction of effect	Impact on recommendations
Chen, X et al (2020)	Systematic review (n=1885)	Metformin	People (no average age reported) with type 2 diabetes, antipsychotic-induced weight gain or obesity	Reports maximal reduction of -8.82% of baseline weight, and to achieve half of this would take 45.5 weeks of treatment	Favours intervention	May impact CG178-1.1.3.2. Possible role for metformin in mitigating AIWG. No info about age of participants, impact on CG155 uncertain
De Silva VU et al (2016)	Systematic review (n=743)	Metformin	People with AIWG	Change in weight vs placebo -3.27 kg, p<0.001. Metformin increased percentage of body weight lost −5.07%, p < 0.001).	Favours intervention	May impact CG178-1.1.3.2. Pooled effects from 2 small studies with children report a reduction that partly addresses CG155 research

				For children (2 studies, n=62) −3.92kg, p < 0.001).		recommendation 5 (RR5).
Ellul, P et al (2018)	Systematic review (n=205)	Metformin	Children and young people <18 years receiving risperidone, aripiprazole, olanzapine, and clozapine for any psychiatric disorder	Vs placebo 4 weeks -0.98 kg (95% CI - 1.26, - 0.69) 12 weeks: - 1.83 kg (95% CI - 2.47, - 1.18) 16 weeks: - 3.23 kg (95% CI - 5.59, - 0.86) Weight change was not significant vs pla at 2 and 8 weeks.	Favours intervention	Addresses CG155-RR5. Suggests a role for metformin in weight management in children receiving second generation antipsychotics. May also impact CG185-1.8.3 (bipolar disorder).
Fitzgerald, I et al (2022)	Guideline about metformin for AIWG (includes systematic review of 9 studies)	Metformin	Adults with psychosis	Key recommendations *If metformin is being used as part of an early intervention strategy, we*	N/A	Limited impact on CG178-1.1.3.2. Guideline not from a guideline producing centre but a coalition of Ireland-based clinicians who

				recommended that plateau of weight gain should be the goal of treatment. Reversal of weight gained to date due to antipsychotic treatment may also be feasible. Strength of recommendation: Strong. Quality of evidence: Moderate		highlight the paucity of interventional recommendations about AIWG.
Khan, MF (2020)	RCT (n=138)	Metformin	People (mean age 29 years, range 17 to 60) with schizophrenia taking olanzapine	Mean weight change: Olanzapine plus metformin =−2.62Kg (+/- 3.13) vs olanzapine only =−1.57Kg (+/- 2.83), Mean difference= 1.05Kg, p=0.04	Favours intervention	Adds to evidence for metformin but alone would not impact CG178. The mean difference is of questionable clinical significance (<1.5% of baseline bodyweight). The study is conducted in Pakistan and

						external validity is questionable.
Mansuri, Z et al (2022)	Systematic review (n=213)	Metformin	Children (11-13 years) taking second generation antipsychotics and metformin for weight gain	Versus placebo weight: mean difference= −2.05kg, 95% CI (−2.81, −1.30), p<0.001 I2 22% (this decrease was slightly larger (-2.28kg) when 1 study containing low BMI baseline participants was excluded). BMI (3 studies): Mean difference= −0.09, 95% CI: (−0.16, −0.03), p<0.001 I2 60%. Metformin associated with nausea and vomiting [OR: 4.07 (1.32–12.54), *p*-value: 0.02] and diarrhoea [OR: 2.93 (1.50–5.71),	Favours intervention	Potential impact on CG155-RR5 about weight mgmt. Suggests a small effect on weight gain attenuation for metformin at 12-16 weeks in children with BMI 26-30. Clinically meaningful? Increased odds of nausea and vomiting in children using metformin and the degree to which it reduces net benefit needs expert input.

				p-value: 0.002]. No difference in dropout rates between metformin and placebo arms.		
Siskind, D et al (2016)	Systematic review (n=478)	Metformin	Adults without diabetes taking clozapine	Versus pla: weight loss= −3.12kg, 95%CI -4.88kg to -1.37kg) BMI change=−1.18kg/m^2, 95%CI -1.76kg/m^2 to -0.61kg/m^2).	Favours intervention	Reports efficacy for metformin with a reasonably large effects size, which adds to evidence for metformin and its impact on CG178. Impact may be limited due to external validity: no participant data from OECD countries (includes from China, Taiwan, Venezuela, Iran).
Zheng, W et al (2019)	Systematic review (n=732)	Metformin-lifestyle intervention combination (MLIC)	Adults with schizophrenia receiving antipsychotics	MLIC vs metformin Weight change (1 RCT, n=64)	Favours intervention	Impact on CG178 questionable due to concerns about external validity. (All includes China-based). Results suggests a role for this combination for

				WMD: − 1.50 kg [95% CI: − 2.98, − 0.02], p=0.05 MLIC versus lifestyle intervention (1 RCT, n=64), WMD: − 3.30 kg [95 % CI: − 4.78, − 1.82], p < 0.0001 MLIC vs placebo Body weight (3 RCTs, n=244) WMD: −5.05 kg [95 % CI: −7.92, −2.18], p = 0.0006, I 2 = 92%, (Less frequent weight gain >7% compared with placebo: RR = 0.31, p < 0.00001, NNH= 3, 95% CI: 2–4).		managing AIWG. PH44-1.19.1 recommends this combination for obese people at risk of diabetes.

Zimbron, J et al (2016)	Systematic review (n=3 studies meta-analysed)	Metformin	Adults receiving clozapine for schizophrenia and metformin for AIWG.	BMI=-0.89kg/m^2 (-1.2 to -0.58) Waist circumference=-1.69cm (-2.84 to -0.54)	Favours intervention	Limited impact on CG178. Improvements in anthropometric outcomes likely not clinically significant. Two of the 3 RCTs in the meta-analysis are also included in the de Silva (2016) above.
Studies about olanzapine/samidorphan combination (OLZ/SAM)						
Correll, CU et al (2023)	RCT (n=538)	OLZ/SAM fixed dose	Adults with schizophrenia and BMI 18-30kg/m^2	Versus olanzapine alone: small (0.6kg/m^2) reduction in BMI and lower prevalence of metabolic syndrome at 24 weeks (vs olanzapine only, NNT=20)	Favours intervention	No impact. OLZ/SAM not licensed in the UK. Did not progress to NICE TA in 2018
Kahn, RS et al (2022)	RCT (n=428)	OLZ/SAM	Young adults (16-39 years) with schizophrenia or bipolar disorder (diagnosis <4	Change in bodyweight from baseline at 12 weeks: olanzapine + samidorphan	Favours intervention	Suggests OLZ/SAM may reduce weight gain. No immediate impact as OLZ/SAM not

			years old), BMI< 30 kg/m^2, and <24 weeks' cumulative antipsychotic exposure	(4.91%) vs olanzapine (6.77%): mean difference=−1.87 % p= 0.012		licensed in the UK. Did not progress to NICE TA in 2018. No evidence of imminent UK licensing applications
Kahn, RS et al (2023)	RCT (n=438)	OLZ/SAM (5-20/10 mg/d)	Young adults (16-39 years) with schizophrenia or bipolar disorder (diagnosis <4 years old), BMI< 30 kg/m^2, and <24 weeks' cumulative antipsychotic exposure.	At 12 weeks =>7% weight gain, OLZ/SAM vs olanzapine 33.1% vs 44.8%; OR = 0.61, 95% CI = 0.39 to 0.94 =>10% weight gain, OLZ/SAM vs olanzapine 21.9% vs 30.4%, OR= 0.64; 95% CI = 0.39 to 1.05	Favours intervention	Suggests OLZ/SAM may reduce clinically significant weight gain. No immediate impact as OLZ/SAM not licensed in the UK. Did not progress to NICE TA in 2018. No evidence of imminent UK licensing applications.
Kahn, RS et al (2021)	RCT extension study, no control (n=168)	OLZ/SAM (5-20/10 mg/d)	As above	57/265 (21.5%) patients experienced clinically significant (=>7%) weight gain at some point during	Favours intervention	Suggests OLZ/SAM gains not sustained at 52 weeks. No immediate impact as OLZ/SAM not licensed in the

				the 52 week study. 56/265 (21.1%) clinically significant weight loss. Proportions the same whether they had received olanzapine plus samidorphan or olanzapine only in preceding trial		UK. Did not progress to NICE TA in 2018. UK licensing applications should be monitored
Meyer, JM et al (2022)	RCT (n=538)	OLZ/SAM	Adult outpatients with schizophrenia receiving antipsychotics with BMI 18-30Kg/m^2 and stable body weight pre-trial entry (=<5% weight change).	Compared with Olanzapine only: odds of gaining at least 10% of baseline body weight OR, 0.50; 95% CI: 0.31, 0.80; *P* = 0.003. P-value significant for males, people aged =>30, black people and baseline BMI of =>27 kg/	Favours intervention	None. Preventing =>10% is a very high threshold for success (=>5% more appropriate?). OLZ/SAM not licensed in the UK. Did not progress to NICE TA in 2018. UK licensing applications should be monitored.

Yagoda, S (2021)	RCT extension, no control (n=277)	OLZ/SAM	Adults with schizophrenia or bipolar I disorder who had received placebo, olanzapine or olanzapine/samid orphan during the ENLIGHTEN-1 trial.	Mean weight change from baseline to week 52 was 1.86 kg (2.79% increase). Discontinuation included patient withdrawal (15.5%), loss to follow-up (6.9%), adverse events (5.8%), lack of efficacy (1.8%). Adverse events (AEs) reported in 136 (49.1%) patients	Favours intervention	None. OLZ/SAM may attenuate weight gain at 52 weeks. Weight increased from baseline less than reported for those receiving antipsychotics (APs) alone. Compliance with treatment for 52 weeks may be an issue (15% withdrawal). Treatment not licensed in the UK. Did not progress to NICE TA in 2018.
Studies about GLP-1 receptor agonists						
Ishoy, PL et al (2017)	RCT (n=45)	Exenatide	Obese adults without diabetes with schizophrenia treated with antipsychotics	Weight change: exenatide group= -2.2 ± 3.3kg vs placebo= -2.2 ± 4.4, p=0.23. BMI: exenatide=−0.8kg /m^2 vs	No difference	No impact. CG155 and CG178 do not make any recommendations about GLP-1 agonists. Superiority for

				placebo=−0.8kg/ m^2, p=0.64.		exenatide not observed.
Larsen, JR et al (2017)	RCT (n=103)	Liraglutide	Adults with schizophrenia who are overweight or obese and have prediabetes.	63.8% (30/47) of liraglutide patients achieved normal glucose tolerance vs 16.0% (8/50) placebo patients, p<0.001. Placebo-deducted weight change from baseline for liraglutide=-−5.3Kg; 95% CI, −7.0 to −3.7 kg.	Favours intervention	Suggests a role for liraglutide which is licensed for weight and diabetes management. CG178-1.1.3.2 cross refers to CG189 which recommends liraglutide for people with a BMI =>35 and prediabetes (CG189 table 1). New evidence supports this recommendation for adults with schizophrenia. Adaptation of CG189's rec for CG178 may be warranted.
Lee, K et al (2022)	Systematic review (11 studies; 8 about liraglutide including 2 high	Liraglutide	Adults with a psychotic disorder receiving a weight loss medication	Versus pla.: Body weight=−5.29kg	Favours intervention	Meta-analysis comprised mostly of participants from Larsen et al

	quality RCTs that were meta-analysed (n=131)).		licensed in the UK, EU or US, to treat AIWG or obesity in schizophrenia	(−6.86 to −3.71) p<0.00001 BMI=−1.69kg/m^2 (−2.99 to −0.4) p=0.01		(2017) above. Suggests a role for liraglutide in adults which is licensed for weight and diabetes management. CG178-1.1.3.2 cross refers to CG189 which recommends liraglutide for people with a BMI =>35 and prediabetes (CG189 table 1). Adaptation of CG189's rec for CG178 may be warranted.
Svensson, CK et al (2019)	RCT (n=87) open label extension study	Liraglutide	Adolescents and adults taking clozapine for schizophrenia previously treated with 16 weeks' of liraglutide	From end of treatment (16 weeks) to 1 year post-treatment - 12 patients in the liraglutide group (29.3%) vs 5 patients in the placebo group (10.9%)	No effect at 1 year	If recommendations are made about liraglutide for AIWG long-term interventions also need to be considered. Liraglutide may reduce risk of

				developed T2D OR 3.31 (95% CI 1.05 to 10.43), p=0.06. From baseline (week 0) the placebo-subtracted body weight loss remained significantly reduced (-3.8 kg, 95% CI: -7.3 to -0.2, P = 0.04) From end of treatment (week 16) to follow-up (1 year post-treatment) +1.5Kg was regained in the liraglutide group (95% CI 1.8 to 4.7), comparable to the placebo group, p=0.38.		weight gain and diabetes, but weight is regained after treatment is stopped. TA664 recommends liraglutide for managing overweight and obesity alongside a reduced-calorie diet and increased physical activity in adults.

Whicher, CA et al (2021)	RCT (n=47)	Liraglutide	Adults with schizophrenia receiving antipsychotics who are also overweight or obese	Placebo-deducted weight loss=-6.0Kg, p=0.015 79% completed the trial	Favours intervention	Limited impact on CG178 and CG185 due to being a small pilot RCT. Adds to evidence for liraglutide's effectiveness in attenuating AIWG. Liraglutide is licensed in the UK as an adjunct for management of weight loss.
Studies about topiramate						
Jamilian, H et al (2018)	RCT (n=59)	Topiramate	Adults with schizophrenia taking olanzapine	BMI: Topiramate=−2.2 kg/m^2 (26.67 to 24.47) vs placebo=−0.15kg/m^2 (27.96 to 27.81), p=0.001	Favours intervention	Limited impact on CG178. Small study conducted in India which observed a small reduction in BMI which is of questionable clinical significance and UK relevance. Adds to evidence for topiramate's efficacy for AIWG (see also Hilluy

						2018, Agarwal 2022). Topiramate is licensed for seizures and migraine prophylaxis. BNF entry carries several MHRA safety alerts. Suggests net benefit may be questionable.
Wang, C et al (2020)	RCT (n=62)	Topiramate (vs metformin)	Adults, some adolescents (mean age 32 years, range 15-55) with schizophrenia taking antipsychotics =>6 months and have gained >10% of their body weight	Weight change from baseline for Topiramate: Mean difference after 16 weeks=-5.36Kg (98.19kg reduced to 92.23Kg), p<0.001 for 4 weeks, 8 weeks, 12 weeks and 16 weeks). Metformin: Mean difference after 16 weeks=-0.92Kg (91.55Kg reduced to 90.63Kg),	Favours topiramate	None. While this reports superiority for topiramate superiority, there is a large difference in baseline BMI between groups and a large dropout rate p None. Although this study reports topiramate superiority there is a large difference in baseline weight between groups

				p>0.05 at all timepoints. Topiramate vs metformin, p<0.05 for weight and BMI.		and a large dropout rate which confound the result. Conducted with participants based in China and of questionable external validity.
Studies about melatonin						
Igwe, SC et al (2018)	Systematic review (n=117)	Melatonin	Adolescents (n=48) and adults (n=69) with schizophrenia or bipolar disorders treated with olanzapine or clozapine.	Versus placebo Weight change: 1.65Kg, CI -3.20, 6.51 - significant heterogeneity, I2=88%. BMI: 0.28Kg/m^2, CI -1.26, 1.82, significant heterogeneity, I2=83%	No difference	No impact. CG155, CG178 and CG185 do not make recommendations about melatonin for weight loss. Superiority for melatonin not observed.

Mostafavi SA et al (2017)	RCT (n=48)	Lithium plus olanzapine plus melatonin	Children and adolescents (11-17 years) with bipolar disorder receiving olanzapine plus lithium	Vs Lithium plus olanzapine plus placebo BMI= 2.45 vs. 3.25, t=1.936; p=0.061. Weight change: 5.8 kg vs. 8.2 kg, t = 1.923; p=0.065	No difference	No impact on CG185 bipolar disorder. No superiority reported for melatonin.
Studies investigating several interventions						
Agarwal, SM et al (2022)	Cochrane Review (n=1388)	Various including metformin, reboexetine/betahistine combination, topiramate, olanzapine/samidorphan combination, monoamine modulators, H2 agonists	Mainly adults with schizophrenia taking antipsychotics	Reboexetine plus betahistine vs pla: for risk of >5% weight gain: risk ratio (RR) 0.27, (95% confidence interval (CI) 0.11 to 0.65); 1 study, 43 participants. Evidence certainty: very low Samidorphan plus olanzapine vs olanzapine alone: for risk of >10% weight gain: RR 0.59, (95% CI	Favours metformin and SAM/OLZ	Potential impact on CG178-1.1.3.2. Largely relevant to adults; suggests metformin may be an option as an adjunct for prevention of AIWG. SAM/OLZ not licensed in UK

				0.43 to 0.81); 1 study, 1 study, 266 participants. Evidence certainty: low Metformin: mean change in weight vs pla −4.03 kg, (95% CI −5.78 to −2.28); I2 = 0%; 4 studies, n=131 (inc.49 children). BMI change vs pla −1.63 kg/m^2, 95% CI -2.96 to -0.29; 5 studies, n=227, Evidence certainty: low		
Al Jumaili, W et al (2022)	Systematic review (9 studies)	Various including metformin	Children and adolescents treated with antipsychotics	Results reported narratively: authors suggest metformin as an antipsychotic adjunct could prevent or mitigate weight gain	Favours metformin	Limited impact on CG155 RR5: no meta-analysis

Hilluy, JC et al (2018)	Systematic review (27 studies)	Metformin (14 studies), topiramate (6), nizatidine (4) and sibutramine (3)	Adults with schizophrenia or bipolar I disorder, prescribed medication for weight gain	Metformin vs pla -3.27 kg (95% CI, -4.49 to -2.06) (12 RCTs mostly with adults, 2 with imputed data from authors of this M-A, n=704) high heterogeneity (82%, p<0.001) Topiramate vs pla SMD: -5.33 kg (95% CI, -7.20 to -3.46) (6 RCTs, 1 with imputed data by the authors of this M-A, n=512) high heterogeneity (86%, p<0.001)	Favours metformin and topiramate	Possible impact on CG178-1.1.3.2. Metformin and topiramate demonstrated a positive effect on weight attenuation. Results should be interpreted with caution due to high heterogeneity. Topiramate is not licensed for management of diabetes or weight. Authors note its mechanism for causing weight loss is unclear
Wang Y et al (2021)	Systematic review (61 studies, n=3467)	Various	Adults with AIWG	Topiramate (WMD -5.4, 95% CI -7.12 to -3.68), Zonisamide (-3.44, 95% CI -6.57 to -0.36),	Favours interventions, particularly metformin and GLP−1As	Possible impact on CG178 and CG185. Adds to evidence for metformin andGLP-1 receptor agonists for managing AIWG. Other

				Metformin (-3.01, 95% CI -4.22 to -1.83), Glucagon-like peptide-1 receptor agonists (GLP-1RAs) (-3.23, 95% CI -5.47 to -0.96), Nizatidine (-2.14, 95% CI -4.01 to -0.27) were significantly superior to placebo.		drugs reported as showing superiority constitute an experimental use. Liraglutide is licensed for weight loss as a monotherapy (with lifestyle interventions) and as a dual therapy with metformin for diabetes. Metformin is licensed for management of diabetes with overweight/obese
Zhuo, C et al (2018)	Systematic review (incl. network meta-analysis, n=1349)	Various	People treated with pharmacological interventions for antipsychotic-induced weight gain	Topiramate MD= −3.07kg (95% CI: -5.57, -0.48); sibutramine MD= −2.97kg (95% CI: -4.18, -1.77); metformin MD=−2.50kg (95% CI: -3.21, -1.80); reboxetine MD= −2.25 kg (95% CI: -3.54, -	Favours topiramate and metformin	Impact on CG178-1.3.1.2 as it suggests effectiveness for topiramate and metformin for attenuating AIWG. They note topiramate associated with AEs.

				0.95); ranitidine was not superior −0.40kg (95% CI: -1.25, 0.45) Rank order: Sibutramine, Topiramate, Metformin, Reboxetine, Ranitidine Excluding studies with <12 months follow-up showed metformin, sibutramine and topiramate effected a consistently significant reduction in body weight: -2.54 (95% CI: -3.29, -1.79), -2.98 (95% CI: -4.34, -1.62), and -2.95 (95% CI: -5.87, -0.03), respectively. Topiramate: risk for adverse		Possible impact on CG155-RR5: data from 3 includes (Canada, Iran, US) from children.

				events, RR=1.88 (95% CI: 0.44, 7.94) but AEs for topiramate and for all interventions were very small. Authors note sibutramine has had its licence revoked in several countries due to reports of adverse effects and caution it should not be used despite the results of this NMA.		
Studies about other pharmacological interventions						
Bai, L et al (2023)	RCT (n=94)	Betahistine hydrochloride	Adults with chronic schizophrenia taking antipsychotics	Not superior to placebo for any outcomes	No difference	None
Gu, Xiao-Jing et al (2018)	Systematic review (n=315)	Ranitidine	Adults with schizophrenia	Versus antipsychotic only: BMI mean	No difference	No impact. Ranitidine as an adjunct to

			taking antipsychotics	difference: −1.08 kg/m^2 (95%CI: −2.15, −0.01); p=0.05; I2 = 94% Weight (WMD): −1.54 kg (95%CI: −3.13, 0.04); I2 = 78% Large heterogeneity between studies.		antipsychotics was not superior to antipsychotics alone.
Moghimi Sarani, E et al (2020)	RCT (n=61)	Sitagliptin	People with schizophrenia receiving olanzapine (10-30mg/d, for at least 1 month)	No difference in BMI or waist circumference between group (p>0.05)	No difference	No impact on CG155 or CG178. Sitagliptin lowered HbA1c but had no effect on anthropometric measures
Zheng, W et al (2017)	Systematic review (n=265)	Amantadine	Adults with schizophrenia taking antipsychotics	Vs pla Weight change: n = 205; WMD −2.22 kg; p=0.001, I = 45% (8.2 +/- 5.9 weeks treatment duration)	Favours intervention	Possible impact on CG178 and CG185; clinical significance? Amantadine is licensed for Parkinson's, herpes zoster and influenza symptoms

						(specific strains) Use in this context seems highly experimental.

Table 2 Lifestyle, behavioural and nutritional supplement interventions for weight management

Studies about lifestyle and behaviour change interventions						
Reference	Study type	Intervention	Population	Result	Direction of effect (vs comparator)	Impact on recommendations
Fernández Guijarro S et al (2019)	RCT (n=61)	Weekly nurse-led community-based lifestyle modification intervention comprising 20 minutes of theory and 60 minutes of physical activity. Duration: 24-weeks	People with serious mental illness	Versus care as usual: no between group difference in weight, waist circumference, fasting glucose, and systolic blood pressure. Differences in BMI, (p=0.010). Increased physical activity	No difference for weight change	None. Schizophrenia and bipolar guidelines make no recommendations about this type of intervention

				reported (p=0.035)		
Holt, RIG et al (2019)	RCT (n=414)	STEPWISE: a theory-based, group structured lifestyle education programme of 12 months' duration. Comprised: 4 weekly 2.5 hour sessions delivered face to face by trained facilitators; followed by 1:1 remote support	Adults with schizophrenia	Difference in weight vs usual care: 0.0 kg, 95% CI-1.6 to 1.7, p=0.963 ICER: £246,921/QALY	No difference	None. Intervention is not superior or cost effective compared to usual care. CG178 does not make any recommendations about condition-tailored lifestyle education programmes for weight loss.
Lee C et al (2022)	Systematic review (n=4305)	Behavioural weight management interventions (BWMIs)	People with serious mental illness	36 different BWMIs identified. Mean BWMI weight loss=−4.37 to +1 kg at 6 weeks to 18 months follow-up vs controls, mean=−1.64 to +3.08 kg.	Favours intervention	The results supports CG189-1.5 to offer behavioural interventions which is cross-referred to by CG178. CG155 does not cross-refer to CG189, and this should

				BWLI effectiveness attributes: regular contact, tools to support enactment, and tailored materials.		be considered as a minimum
Loojimans, A et al (2019)	RCT with nested economic analysis (n=244)	Twelve-month multimodal lifestyle approach. Using a web tool, nurses trained in motivational interviewing assisted patients in assessing their lifestyle behaviours, creating a risk profile and constructing lifestyle goals, discussed during fortnightly regular care visits.	Adults with a serious mental health condition	Waist circumference vs care as usual: 6 months follow-up=−0.15 cm (95%CI: - 2.49; 2.19) 12 months follow-up=−1.03 cm (95%CI: - 3.42; 1.35), p>0.05.	No difference	None. CG178 does not make recommendations specifically about lifestyle interventions but cross refers to CG189 which does. CG189-1.4.2 recommends to account for comorbidities when choosing lifestyle interventions. Adaptation of CG189 recs for CG178 or more specific cross-

						referrals should be considered.
Loojimans, A et al (2020)	RCT with nested economic analysis (n=244)	As above	As above	QALYs did not differ between groups; low probability of cost effectiveness	No difference	None
O'Donoghue, B et al (2022)	RCT (n=77)	Physical health nurse integrated into treatment as usual (TAU)	Young people with first episode psychosis	Weight gain of =>7% vs TAU alone: 12 weeks, odds ratio=0.72, 95% CI 0.25-2.06, P = 0.54 (27.3% intervention group vs 34.4% TAU group). 6 months, 40.7% intervention group vs 44.1% of the TAU group (P = 0.79).	No difference	None. No recommendations are made about the use of 'physical health nurses' or similar in psychosis or bipolar guidelines.
Romain AJ et al (2020)	Systematic reviews (n=2128)	Motivational theory-based interventions (MTBIs) aimed at increasing physical activity	People with severe mental illness	Vs comparators: Physical activity: g=0.27, 95% CI [0.03; 0.51], *p* = .003)	Favours intervention	Reports a small but positive effect for MTBIs. CG178, CG185 and CG155 make no recommendations about

				Weight change: WMD = −1.87 kg, 95%CI [−2.98; −0.76], *p* =0 .001) BMI: WMD = −0.82 kg/ m^2, 95%CI [−1.23; −0.41], *p* = 0.009)		motivational-theory-based interventions. CG189, which is cross-referred to by CG178 and CG185, contains behavioural recommendations in section 1.5 that include goal setting and stimulus control that accommodate motivational theory. This adds to evidence that CG155 should at least make a cross-referral to CG189 and possibly PH44 physical activity.
Soric T et al (2019)	RCT (n=76)	Dietary Approaches to Stop Hypertension (DASH) diet (hospital-	Hospitalised schizophrenic patients with metabolic	Prevalence of MetS in DASH group at follow-up=75.8%, p=0.002, and in treatment as	No difference	None. No guidelines about schizophrenia or bipolar recommend this

		based dietary programme)	syndrome (MetS)	usual=67.7%, p=0.0003, odds ratio=0.9; 95% confidence interval =0.43-1.87. No statistically significant difference		type of inpatient diet
Speyer, H et al (2019)	Systematic review (n=4267)	Lifestyle interventions about weight management in people with serious mental illness (SMI)	People with SMI	BMI: -0.63 kg/m^2 95% CI-1.02 to -0.23; p = 0.002; I2 = 70.7% vs controls (significance not sustained for studies with longer follow-uptimes). Risk ratio for losing =>5% of baseline body weight=1.51, 95% CI =1.07-2.13; p=0.02 vs controls	Favours intervention	Limited impact as schizophrenia and bipolar guidelines make no recs about lifestyle interventions or cross-refer to CG189 obesity. Authors report that while there is an effect for lifestyle interventions in the short term, clinical significance of the effects size is questionable.

Sugawara, N et al (2018)	RCT (n=265)	Nutritional education group Dietary advice given by a doctor.	Adults with schizophrenia who are obese	Prevalence of MetS vs standard care: Doctor's dietary advice=68.9%, nutritional advice=67.2%; standard care=47.5% Interventions superior to standard care but not each other	Favours interventions	Supports CG178-1.1.3.2 which cross refers to CG189 which recommends (1.7.1) tailoring dietary changes to food preferences and allowing for a flexible and individual approach to reducing calorie intake. Study conducted in Japan where thresholds for MetS may be different than the UK: external validity is questionable.
Teasdale, SB (2017)	Systematic review (20 studies; 13 about people with schizophrenia spectrum	Nutrition interventions	People with schizophrenia spectrum or bipolar disorders	Weight (19 studies): Hedges *g*=−0.39, 95% CI −0.56 to −0.21, *P*<0.001, *I* 2 = 55% (mean difference in kg=	Favours interventions	Supports recommendations CG189-1.7.1-1.7.2. CG189 is cross-referred to by CG178

	disorders; 7 bipolar disorder)			-2.71Kg, p<0.001) BMI (17 studies): Hedges *g*= −0.39, 95% CI −0.56 to −0.22, *P*<0.001, *I* 2 = 51% (mean difference in kg/m^2=-0.870, p<0.001). Larger effects size observed if delivered by a dietician or nutrition professional (p<0.001)		
Young, AS (2021)	RCT (n=276)	Online weight management plus peer coaching (WebMOVE) Face to face weight management coaching (MOVE)	Overweight adults with serious mental illness (SMI)	Very little difference in change in BMI between interventions and care as usual. Subgroup analysis 52/200 obese participants	No difference (may favour intervention for obese subgroup)	Small effect for WebMOVE. Supports recommendations in CG189 to provide tailored lifestyle interventions which is cross-referred to by CG178 and

				probability of losing =>5% body weight found that the probability of losing =>5% of weight and highest for WebMOVE ($\chi 2 = 6.4$; $p = 0.04$)		CG185. The study does not correlate antipsychotic intake with the effect of WebMOVE
Studies about supplements						
Huang, J et al (2022)	RCT (n=136)	Probiotics + dietary fibre (P+DF) P or DF alone	Adults receiving atypical antipsychotics with a diagnosis of schizophrenia or bipolar disorder	Weight difference (Kg) from baseline (mean at baseline=70.99) P+DF= −2.36kg, Palone=−0.56kg DFalone=−0.34kg All superior to Pla, (+2.36kg	Favours interventions	No impact on CG178 or CG185 (bipolar) which make no recommendations about supplements for weight loss. Favours combination of dietary fibre plus probiotic over individual interventions alone for weight reduction and

				gain) P+DF vs DF, p=0.026 P+DF vs P, p=0.05 DF vs P, p>0.05		BMI. Study conducted in China with participants with low baseline weights. Relevance to an NHS setting is questionable.
Huang J et al (2022a)	RCT (results from 2 RCTs probiotics n=66; dietary fibre n=58)	Olanzapine plus probiotics Olanzapine plus dietary fibre	Antipsychotic naïve adults with first episode psychosis taking olanzapine	Olanzapine plus probiotic: weight change at 12 weeks= −1.74Kg, CI −3.79, 0.31, p=0.095 BMI at 12 weeks= −0.45Kg/m^2, CI−1.29, 0.38, p=0.284 Olanzapine plus dietary fibre: weight change at 12 weeks= −3.45Kg, CI−5.91, −1.00, p=0.007	Favours olanzapine plus dietary fibre only	No impact on CG178 or CG155, CG185 which make no recommendations about probiotics or dietary fibre. This paper reports a positive result for olanzapine plus dietary fibre in a small number of people (n=58). Participants have very low baseline weights probably due to their South Asian ethnicity which reduces the relevance of

				BMI at 12 weeks=−1.26Kg/m^2, CI−2.28, −0.24, p=0.016		the results to a UK setting

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